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 PRACTICAL LESSONS IN EDUCATIONAL DISCIPLINE

International Faculty, V-th course

Educational discipline: **Internal Medicine**

Approved

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Practical Lessons #1-2

Topic 1: Rheumatic fever

Aim: To teach applicants to master the method of examination of patients with systemic connective tissue diseases with the selection of the main rheumatologic syndromes. To study probable etiological and predisposing factors, pathogenesis of acute rheumatic fever, main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis, methods of primary and secondary prophylaxis.

Basic definitions:

№	Term	Definition
1.	Carditis	Inflammation of the heart. It is usually studied and treated by specifying it as: *pericarditis* – is the inflammation of the pericardium; *myocarditis* – of the heart muscle; *endocarditis* – of the endocardium; *pancarditis* – is the inflammation of the entire heart: the pericardium, the myocardium and the endocardium
2.	Erythema marginatum	A long-lasting reddish rash that begins on the trunk or arms as macules, which spread outward and clear in the middle to form rings, which continue to spread and coalesce with other rings, ultimately taking on a snake-like appearance. This rash typically spares the face and is made worse with heat.
3.	Sydenham's chorea	A characteristic series of involuntary rapid movements of the face and arms (St. Vitus' dance). This can occur very late in the disease for at least three months from onset of infection.
4.	Streptococcus pyogenes	Gram-positive, aerotolerant bacteria in the genus Streptococcus. These bacteria are extracellular, and made up of non-motile and non-sporing cocci that tend to link in chains. They are clinically important for humans, as they are an infrequent, but usually pathogenic, part of the skin microbiota that can cause Group A streptococcal infection. S. pyogenes is the predominant species harboring the Lancefield group A antigen, and is often called group A
5.	Anti-streptolysin O	Antibody made against streptolysin O, an immunogenic, oxygen-labile streptococcal hemolytic exotoxin produced by most strains of group A and many strains of groups C and G Streptococcus bacteria. The "O" in the name stands for oxygen-labile; the other related toxin being oxygen-stable streptolysin-S. The main function of streptolysin O is to cause hemolysis, in particular, beta-hemolysis.

Rheumatic fever is a nonsuppurative, acute inflammatory complication of group A streptococcal infection, causing combinations of arthritis, carditis, subcutaneous nodules, erythema marginatum, and chorea. Diagnosis is based on applying the Jones criteria to information gleaned from history, examination, and laboratory testing. Treatment includes aspirin or other NSAIDs, corticosteroids during severe carditis, and antimicrobials to eradicate residual streptococcal infection and prevent reinfection.

A first episode of acute rheumatic fever (ARF) can occur at any age but occurs most often between 5 yr and 15 yr and is uncommon before 3 yr and after 21 yr. Therefore, testing for group A streptococcal (GAS) infection for primary prevention of rheumatic fever is usually not necessary in patients < 3 yr with pharyngitis.

Pathophysiology

GAS infection is the etiologic precursor of ARF, but host and environmental factors are important. GAS M proteins share epitopes (antigenic-determinant sites that are recognized by antibodies) with proteins found in synovium, heart muscle, and heart valve, suggesting that molecular mimicry contributes to the arthritis, carditis, and valvular damage. Genetic host risk factors include the D8/17 B-cell antigen and certain class II histocompatibility antigens. Undernutrition, overcrowding, and lower socioeconomic status predispose to streptococcal infections and subsequent episodes of rheumatic fever.

The joints, heart, skin, and CNS are most often affected. Pathology varies by site.

Joints:

Joint involvement manifests as nonspecific inflammation in a synovial biopsy specimen, sometimes with small foci resembling Aschoff bodies (granulomatous collections of leukocytes, myocytes, and interstitial collagen).

Heart:

Cardiac involvement manifests as carditis, typically affecting the heart from the inside out, ie, valves and endocardium, then myocardium, and finally pericardium. It is sometimes followed years later by chronic rheumatic heart disease, primarily manifested by valvular stenosis, but also sometimes by regurgitation, arrhythmias, and ventricular dysfunction. Aschoff bodies often develop in the myocardium and other parts of the heart. Fibrinous nonspecific pericarditis, sometimes with effusion, occurs only in patients with endocardial inflammation and usually subsides without permanent damage. Characteristic and potentially dangerous valve changes may occur. Acute interstitial valvulitis may cause valvular edema. Left untreated, valve thickening, fusion, and retraction or other destruction of leaflets and cusps may result, leading to stenosis or insufficiency. Similarly, chordae tendineae can shorten, thicken, or fuse, adding to regurgitation of damaged valves or causing regurgitation of an otherwise unaffected valve. Dilation of valve rings may also cause regurgitation. The mitral, aortic, tricuspid, and pulmonic valves are affected, in order of decreasing frequency. Regurgitation and stenosis are the usual effects on the mitral and tricuspid valves; the aortic valve generally becomes regurgitant initially and stenotic much later.

Skin:

Subcutaneous nodules appear indistinguishable from those of RA, but biopsy shows features resembling Aschoff bodies. Erythema marginatum differs histologically from other skin lesions with similar macroscopic appearance, eg, the rash of systemic juvenile idiopathic arthritis (JIA), Henoch-Schönlein purpura, erythema chronicum migrans, and erythema multiforme. Perivascular neutrophilic and mononuclear infiltrates of the dermis occur.

CNS:

Sydenham's chorea, the form of chorea that occurs with ARF, manifests in the CNS as hyperperfusion and increased metabolism in the basal ganglia. Increased levels of antineuronal antibodies have also been shown.

Symptoms and Signs

An initial episode of symptoms occurs typically about 2 to 4 wk after the streptococcal infection. Manifestations typically involve some combination of the joints, heart, skin, and CNS.

Joints:

Migratory polyarthritis is the most common manifestation, occurring in about 70% of children; it is often accompanied by fever. Occasionally monarthritis occurs. Joints become extremely painful and tender and may be red, hot, and swollen. Ankles, knees, elbows, and wrists are usually involved. Shoulders, hips, and small joints of the hands and feet also may be involved, but almost never alone. If vertebral joints are affected, another disorder should be suspected.

Arthralgia-like symptoms may be due to nonspecific myalgia or tenodynia in the periarticular zone; tenosynovitis may develop at the site of muscle insertions. Joint pain and fever usually subside within 2 wk and seldom last > 1 mo.

Heart:

Carditis can occur alone or in combination with pericardial rub, murmurs, cardiac enlargement, or heart failure. In the first episode of ARF, carditis occurs in about 50%. Patients may have high fever, chest pain, or both. In about 50% of cases, cardiac damage (ie, valve dysfunction) occurs much later.

Murmurs are common and, although usually evident early, may not be heard at initial examination; in such cases, repeated examinations are recommended to determine the presence of carditis. The soft diastolic blow of aortic regurgitation and the presystolic murmur of mitral stenosis may be difficult to detect. Murmurs often persist indefinitely. If no worsening occurs during the next 2 to 3 wk, new manifestations of carditis seldom follow. ARF typically does not cause chronic, smoldering carditis. Scars left by acute valvular damage may contract and change, and secondary hemodynamic difficulties may develop in the myocardium without persistence of acute inflammation.

Heart failure caused by the combination of carditis and valvular dysfunction may cause dyspnea without rales, nausea and vomiting, a right upper quadrant or epigastric ache, and a hacking, nonproductive cough. Marked lethargy and fatigue may be early manifestations of heart failure.

Skin:

Cutaneous and subcutaneous features are uncommon and almost never occur alone, usually developing in a patient who already has carditis, arthritis, or chorea.

Subcutaneous nodules, which occur most frequently on the extensor surfaces of large joints, usually coexist with arthritis and carditis. About 2% of children with ARF have nodules. Ordinarily, the nodules are painless and transitory and respond to treatment of joint or heart inflammation.

Erythema marginatum is a serpiginous, flat or slightly raised, nonscarring, and painless rash. About 2% of children have this rash. It sometimes lasts < 1 day. Its appearance is often delayed after the inciting streptococcal infection; it may appear with or after the other manifestations of rheumatic inflammation.

CNS:

Sydenham's chorea occurs in about 10% of children. It may develop along with other manifestations but frequently arises after the other manifestations have subsided (often months after the acute streptococcal infection). Onset of chorea is typically insidious and may be preceded by inappropriate laughing or crying. Chorea consists of rapid and irregular jerking movements that may begin in the hands but often becomes generalized, involving the feet and face. Characteristic findings include fluctuating grip strength (milkmaid's grip), tongue darting (the tongue cannot protrude without darting in and out), facial grimacing, and explosive speech with or without tongue clucking. Associated motor symptoms include loss of fine motor control, and weakness and hypotonia (that can be severe enough to be mistaken for paralysis).

Obsessive-compulsive behavior develops in many patients.

Other:

Fever and other systemic manifestations such as anorexia and malaise can be prominent but are not specific. ARF can occasionally manifest as FUO until a more identifiable sign develops. Abdominal pain and anorexia can occur because of the hepatic involvement in heart failure or because of concomitant mesenteric adenitis. Because of the fever, elevated WBC count, and abdominal guarding, the situation may resemble acute appendicitis, particularly when other rheumatic manifestations are absent. Epistaxis occurs in about 4% of children with an initial episode and in 9% of those with a recurrence. Both abdominal pain and epistaxis were minor manifestations in earlier versions of the Jones criteria.

Prolonged episodes of ARF (> 8 month) occur in about 5% of patients, with spontaneous recurrences of inflammation (clinical and laboratory manifestations) unrelated to intervening streptococcal infection or to cessation of anti-inflammatory therapy. Recurrences usually mimic the initial episode.

Diagnosis

- Jones criteria (for initial diagnosis)
- Testing for GAS (culture, rapid strep test, or antistreptolysin O and anti-DNase B titers)
- ECG
- ESR and C-reactive protein (CRP) level

Diagnosis of a first episode of ARF is based on the modified Jones criteria. The Jones criteria should not be used to establish a recurrence.

A preceding streptococcal infection is suggested by a recent history of pharyngitis and is confirmed by a positive throat culture, an increase in the antistreptolysin O titer, or a positive rapid GAS antigen test. Recent scarlet fever is highly suggestive. Throat cultures and rapid antigen tests are often negative by the time ARF manifests, whereas titers of antistreptolysin O and other antibodies typically are peaking. Only 80% of children with a prior infection have a significantly elevated antistreptolysin O titer; therefore, anti-DNase B antibody level should also be obtained.

Joint aspiration may be needed to exclude other causes of arthritis (eg, infection). The joint fluid is usually cloudy and yellow, with an elevated WBC count composed primarily of neutrophils; culture is negative. Complement levels are usually normal or slightly decreased, compared with decreased levels in other inflammatory arthritis.

ECG is done during the initial evaluation. An echocardiogram and a repeat ECG are done at the time of diagnosis. Serum cardiac marker levels are obtained; normal cardiac troponin I levels exclude prominent myocardial damage. ECG abnormalities such as PR prolongation do not correlate with other evidence of carditis. Only 35% of children with ARF have a prolonged PR interval. Other ECG abnormalities may be due to pericarditis, enlargement of ventricles or atria, or arrhythmias. Echocardiography can detect evidence of carditis in many patients. Chest x-rays are not routinely done but can detect cardiomegaly, a common manifestation of carditis in ARF. Biopsy of a subcutaneous nodule can aid in early diagnosis, especially when other major clinical manifestations are absent. Rheumatic carditis must be distinguished from congenital heart disease and endocardial fibroelastosis; echocardiography or coronary angiography can be used to verify difficult diagnoses.

ESR and serum CRP are sensitive but not specific. The ESR is often > 12 mm/h. CRP is often > 2 mg/dL; because it rises and falls faster than ESR, a normal CRP may confirm that inflammation is resolving in a patient with prolonged ESR elevation after acute symptoms have subsided. In the absence of carditis, ESR usually returns to normal within 3 mo. Evidence of acute inflammation, including ESR, usually subsides within 5 mo in uncomplicated carditis. The WBC count reaches 12,000 to 20,000/μL and may go higher with corticosteroid therapy.

The differential diagnosis includes JIA (especially systemic JIA and, less so, polyarticular JIA), Lyme disease, reactive arthritis, arthropathy of sickle cell disease, leukemia or other cancer, SLE, embolic bacterial endocarditis, serum sickness, Kawasaki disease, drug reactions, and gonococcal arthritis. These are frequently distinguished by history or specific laboratory tests. The absence of an antecedent GAS infection, the diurnal variation of the fever, evanescent skin rash, and prolonged symptomatic joint inflammation usually distinguish systemic JIA from ARF.

Modified Jones Criteria for a First Episode of Acute Rheumatic Fever

Manifestations	**Specific Finding**
Major	Carditis Chorea Erythema marginatum Polyarthritis Subcutaneous nodules
Minor	Arthralgia Elevated ESR or C-reactive protein Fever

	Prolonged PR interval (on ECG)
Diagnosis of acute rheumaticfever requires 2 major or 1 major and 2 minor manifestations and evidence of group A streptococcal infection (elevated or rising antistreptococcal antibody titer [eg, antistreptolysin O, anti-DNase B], positive throat culture, or positive rapid antigen test).	

Degree of RF activity

I degree	*II degree*	*III degree*
Early monosyndromal signs are typical. Indolent carditis is often observed. Neurological disorders, persistent arthralgias are common. **Imaging Studies:**cardiomegaly. **Other Tests:** coronary circulation disturbances, signs of myocardiosclerosis, arrhythmia (in recurrent rheumocarditis) are typical. **Lab Studies:** slightly elevated or normal ESR; C-reactive protein is not found or it is I plus; slightly elevated or normal gamma-globulin level; the values yielded by diphenylamine test are normal; the values of yielded by seromucoid test are also normal; titres of ASO, ASK, ASG are normal.	High temperature is an early clinical manifestation. Carditis may be associated with circulation disturbances of the 1^{st} and 2^{nd} degree. Early symptoms of polyarthritis, monooligoarthritis and chorea may be observed. **Imaging Studies:**cardiomegaly. **Other Tests:** arrhythmia, prolonged PQ interval, coronary circulation disturbances. **Lab Studies:** neutrophil leukocytosis $8*10^9$ - $10*10^9$; ESR – 20 – 40 mm/h. C-reactive protein is I – III plus; the amount of alfa2-globulins is 11 – 16%; the amount of gamma-globulins is up to 21 – 23%; the values yielded by diphenylamine test are 0.25 – 0.3; the values yielded by seromucoid test are 0.3 – 06; 1.5 elevation of ASO, ASK, ASG titres.	Fever is considered to be the major clinical manifestation. Other findings include: migrating polyarthritis, diffuse myocarditis, pancarditis. Some symptoms of pleuritis, peritonitis, rheumatic pneumonia, glomerulonephritis, subdermal nodules, erythema annulare, and chorea are typical. **Imaging Studies:**cardiomegaly, decreased contractility of the myocardium. **Other Tests:** arrhythmia and conduction disturbances. **Lab Studies:** neutrophil leukocytosis is higher than $10,0*10^9$; ESR is more than 40 mm/h; C-reactive protein is III – IV plus; fibrinogen is more than 9-10 g/l; the values yielded by seromucoid test are more than 0.6; the values yielded by diphenylamine test are more than 0.35 – 0.5; the amount of alfa2-globulins is 17%; the amount of gamma-globulins is more than 23 – 25%; titres of ASO, ASG, ASK are 3 – 5 times higher than normal.

Prognosis

Prognosis depends mostly on the severity of the initial carditis. Patients with severe carditis during the first episode may have residual heart disease that is often worsened by the rheumatic fever recurrences to which they are particularly susceptible. Murmurs eventually disappear in about half of patients whose acute episodes were manifested by mild carditis without major cardiac enlargement or decompensation. Risk of recurrent inflammation is intermediate, between the low risk of those without carditis and the high risk of those with a history of severe carditis, but recurrences may cause or worsen permanent cardiac damage. Patients who did not have carditis are less likely to have recurrences and are unlikely to develop carditis if ARF recurs. Sydenham's

chorea usually lasts several months and resolves completely in most patients, but about one third of patients have recurrences. All other manifestations subside without residual effects.

Treatment

- Aspirin or another NSAID
- Sometimes corticosteroids
- Antibiotics

The primary goals are suppression of inflammation and relief of acute symptoms, eradication of GAS infection, and prophylaxis against future infection to prevent recurrent heart disease.

Patients should generally limit their activities if symptomatic with arthritis, chorea, or heart failure. In the absence of carditis, no physical restrictions are needed after the initial episode subsides. In asymptomatic patients with carditis, strict bed rest has no proven value.

Aspirin controls fever and pain caused by arthritis and carditis. The dose is titrated upward until clinical effectiveness is attained or toxicity supervenes. The starting dose for children and adolescents is 15 mg/kg po qid. If not effective overnight, the dosage is increased to 22.5 mg/kg qid the next day and 30 mg/kg qid on the next. Salicylate toxicity is manifested by tinnitus, headache, or hyperpnea and may not appear until after 1 wk. Salicylate levels are measured only to manage toxicity and should not be done until the patient has been receiving aspirin for 5 days. Enteric-coated, buffered, or complex salicylate molecules provide no advantage. Other NSAIDs can be used. For example,naproxen 7.5 to 10 mg/kg po bid is as effective as aspirin.

If a therapeutic effect has not occurred after the 4th day, which is sometimes the case if carditis or arthritis is severe, NSAIDs should be abandoned in favor of a corticosteroid.

Prednisone 0.25 to 1 mg/kg po bid (or 0.125 to 0.5 mg/kg po qid) up to 60 mg/day is recommended. If inflammation is not suppressed after 2 days, an IV corticosteroid pulse of methylprednisolone succinate (30 mg/kg IV once/day, maximum 1 g/day, for 3 successive days) may be given. Oral corticosteroids are given until ESR has remained normal for 1 wk and then are tapered at the rate of 5 mg every 2 days. To prevent worsening of inflammation during the corticosteroid taper, NSAIDs are begun simultaneously and continued until 2 wk after the corticosteroid has been stopped. Inflammatory markers such as ESR and CRP are used to monitor disease activity and response to treatment.

Recurrences of cardiac inflammation (indicated by fever or chest pain) may subside spontaneously, but NSAIDs or corticosteroids should be resumed if recurrent symptoms last longer than a few days or if heart failure is uncontrolled by standard management (eg, diuretics, ACE inhibitors, β-blockers, inotropic agents). In patients with prolonged, recurrent episodes of carditis, immunosuppressants may be effective. Although useful in the acute episode, NSAIDs and corticosteroids do not prevent or reduce long-term valve damage.

Although poststreptococcal inflammation is well developed by the time ARF is detected, antibiotics are used to eradicate any lingering organisms and to prevent reinfection.

Antibiotic prophylaxis:

Antistreptococcal prophylaxis should be maintained continuously after the initial episode of ARF to prevent recurrences. Antibiotics taken orally are just as effective as those given by injection. With the oral route, painful injections are avoided, and clinic visits and observation for postinjection reactions are not needed. With the IM route, adherence difficulties of taking a pill once or twice daily are avoided. The IM regimen has been the standard against which other regimens are measured.

The optimal duration of antistreptococcal prophylaxis is uncertain. Children without carditis should receive prophylaxis for 5 yr or up to age 21 (if the patient turns 21 before 5 yr of prophylaxis is completed). The American Academy of Pediatrics recommends that those with carditis without evidence of residual heart damage receive prophylaxis for 10 yr. Children with carditis and evidence of residual heart damage should receive prophylaxis for > 10 yr; many experts recommend that such patients continue prophylaxis indefinitely. Some experts believe prophylaxis should be

life long in all patients with chorea and should continue in all patients who have close contact with young children because of their high rate of GAS carriage.

Recommended Prophylaxis Against Recurrent Group A Streptococcal Infection

Regimen	Drug	Dose
Standard	Penicillin G benzathine	1.2 million units IM q 3–4 wk* ≤ 27 kg: 600,000 units IM q 3–4 wk*
Alternatives (eg, for patients unwilling to receive injections)	Penicillin V or Sulfadiazine	250 mg po bid ≤ 27 kg: 500 mg po once/day > 27 kg: 1 g po once/day
For patients allergic to penicillin and sulfadiazine	Erythromycin	250 mg po bid
*In developing countries, IM prophylaxis q 3 wk is superior to q 4 wk.		

The American Heart Association no longer recommends that patients with known or suspected rheumatic valvular disease (who are not currently taking prophylactic antibiotics) take short-term antibiotic prophylaxis against bacterial endocarditis for dental or oral surgical procedures.

Equipment: training room, cardiac patient examination simulator Harvey, 6-channel electrocardiograph CARDIOLINE, Echocardiography machine.

Lesson duration: 4 hours

Plan

1. Organizational moment (greetings, checking the audience, the message of the topic, the purpose of the lesson, the motivation of applicants to study the topic).
2. Control of basic knowledge (initial survey with tests of the STEP 2 format – attached, check of workbooks on the topic):
2.1. Requirements for theoretical readiness of applicants to perform practical classes.
Knowledge requirements:

- Definition of rheumatic fever
- Current views on the etiology and pathogenesis of rheumatic fever
- Classification of rheumatic fever
- Clinical presentation of rheumatic fever
- Diagnostic of rheumatic fever, Jones criteria
- Differential diagnostic
- Complications of rheumatic fever
- Treatment of rheumatic fever
- Prognosis for patients with rheumatic fever
- Primary and secondary prophylaxis of rheumatic fever

List of didactic units:

- to collect in detail the anamnesis of the disease;
- to conduct a physical examination of the patient, to identify and assess changes in his condition;
- make a plan for additional examination, evaluate its results;
- formulate and substantiate a preliminary and clinical diagnosis of rheumatic fever, taking into account the severity of disorders according to the classification, comprehensive assessment of patients;

- assessment of possible complications of rheumatic fever;
- evaluation of the results of general clinical examination, laboratory analysis of blood, data of electrocardiogram, echocardiogram, X-rays, CTs, MRIs, ultrasound, etc.

2.2. Questions (tests, tasks, clinical cases) to test basic knowledge on the topic of the lesson:

The tests for self-control with standard answers.

1. A 28-year-old woman has been told she has rheumatic heart disease, specifically mitral stenosis. Which of the following murmurs is most likely present?

A. Pansystolic over all heart area
B. Diastolic rumble at apex of the heart
C. Early diastolic decrescendo at right upper sternal border
D. Holosystolic murmur at apex
E. Late-peaking systolic murmur at right upper sternal border

2. A 17 y.o. patient complains of shortness of breath, palpitation, general weakness, increasing of body temperature up to 37,1 – 37,3C, palpitation. Three weeks ago the man was diagnosed quinsy. On physical examination: heart sounds are arrhythmic, extrasystoles, mitral mild diastolic murmur. Choose the most likely causative agent:

A. Pneumococcus
B. Streptococcus viridans
C. Staphylococcus aureus
D. Streptococcus haemolyticus
E. Adenovirus

3. A 17 y.o. patient complains of dull pain in the heart area without irradiation, shortness of breath and palpitation with exercise. Objectively: temperature – 37.8C, heart rate - 96 per minute, soft systolic murmur at apex. ECG: interval PQ = 0.24 sec. In blood: ESR - 28 mm/h. Which investigation should be carried out to establish the etiology of the disease?

A. Blood cultures for sterility
B. Troponin T
C. Antibodies to streptococci
D. CRP
E. Fibrinogen

Clinical case with standards answers:

CLINICAL CASE # 1

Patient S., aged 52, was admitted to the hospital complaining of shortness of breath, heart palpitations, periodic pain in the heart, gravity in the right hypochondrium, swelling of legs, more in the evening.

He became ill in the age 14 , when three weeks after tonsillitis have a general weakness, fever, pain and swelling in the knee joints. Was diagnosed: Acute rheumatic fever.

At admission: apex beat is palpated in the VI intercostal space. On Botkin's point and II intercostal space on the right systolic and diastolic murmur. Systolic murmur is rude, irradiated on carotid arteries. Palpation determined systolic murmur in II intercostal space to the right of the sternum. I and II sounds weakened.

Formulate a diagnosis

Plan of investigation.

Which are the radiological signs may help in diagnosis?

Your approach to treatment.

Answering standards

1. Recurrent rheumatic fever, inactive phase. Carditis. Combined aortic valve defect. HF II A.

2. ECG, echocardiogram, x-rays of the heart with contrast of the esophagus, blood count, rheumatic tests, ASLO, CRP, seed from the pharynx.

3. Aortic configuration: Increase the first and fourth arch on the left contour of the heart. Waist heart underlined.

4. Cardiac glycosides: digoxin 0, 00025g № 50, 1t. morning, Diuretics: indapamide 2,5 mg № 30, 1t morning; furosemide t.0, 04g № 50, 1t morning, fasting, amp.2ml 1% p-pa (0,02 g), in / jet on 2-4ml; veroshpiron t.0, 025mg № 30, of 1t1-2 times a day. ACE inhibitors: ramipril t 2.5 mg, 5 mg № 20, 2,5 mg, 1 time a day.

III. Formation of professional skills, abilities (mastering the skills of curation, determining the treatment regimen):

1.1. Content of tasks:

Recommendations for tasks: (professional algorithms):

Work at the patient's bedside (according to the algorithm of communication between students and patients).

When examining patients, students must follow the following communication algorithms:

Collection of complaints and anamnesis in patients with internal diseases

1. Friendly facial expression, smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Collection of complaints and medical history of the patient.
5. Explanation of survey results.
6. Explanation of actions (hospitalization, conducting certain examinations) that are planned to be performed in the future.
7. End the conversation.

Physical methods of examination of patients with internal diseases

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Explain to the patient which examination will be performed and obtain his consent.
6. Warning about the possibility of unpleasant feelings during the examination.
7. Preparation for the examination (clean warm hands, trimmed nails, warm phonendoscope, if necessary - use a screen).
8. Conducting an examination (demonstration of clinical skills).
9. Explanation of survey results.
10. End the conversation.

Reporting the results of the examination to patients with internal diseases.

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the results of a particular examination.
5. Involve the patient in the interview (compare the results of this examination with previous results, find out if they understand your explanations).
6. End the conversation.

Planning and forecasting the results of conservative treatment:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.

4. Correct and accessible to the patient's understanding explanation of the need for prescribed treatment.

5. Involvement of the patient (emphasis on the peculiarities of the drugs, duration of administration, possible side effects; find out whether the patient understands your explanations).

6. End the conversation.

Treatment prognosis message:

1. A friendly expression on the doctor's face, a smile.

2. Gentle tone of conversation.

3. Greetings and introductions, expression of interest, respect and care.

4. Correct and accessible to the patient's understanding explanation of the expected results of the prescribed treatment.

5. Involve the patient in the conversation (emphasis on the importance of continuous treatment, adherence to the prescribed treatment regimen, finding out whether your explanations are clear to the patient).

6. End the conversation.

Work 1.

1. Collection of complaints, anamnesis, examination of a patient with acute rheumatic fever.

2. Detection of clinical symptoms.

3. Grouping of symptoms into syndromes.

4. Definition of the leading syndrome.

5. Interpretation of laboratory and instrumental data (clinical analysis of blood, urine, biochemical analysis of blood, chest X-ray or chest CT-scan, X-ray of joints or MRI or ultrasound of joints, ECG, echocardiography, etc.).

6. Carrying out of the differential diagnosis with other arthritis and other heart diseases.

7. Formulation of the clinical diagnosis.

8. Determining the degree of disability.

Work 2.

Appointment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the cathedral library with thematic literature.

The student fills in the protocol of examination of the patient in writing. An example of the initial examination of the patient is attached.

Control materials for the final stage of the lesson:

Tasks for self-control with answers.

1. A 43 y.o. woman complains of shooting heart pain, dyspnea, irregularities in the heart activity, progressive fatigue during 3 weeks. She had acute respiratory disease a month ago. On examination: BP 120/80 mmHg, heart rate 98 bpm, heart boarders enlarged +1,5 cm to the left side, sounds are muffled, soft systolic murmur at apex and Botkin's area; periodically – premature complexes. Liver isn't palpated, there are no edema. Blood test: WBC 6,7*10^9/L, ESR 21 mm/h. What is the most probable diagnosis?

A. Hypertrophic cardiomyopathy

B. Climacteric myocardiodystrophia
C. Ichemic heart disease, angina pectoris
D. Rheumatism, mitral insufficiency
E. Acute myocarditis

2. A 14 year old patient complains of chest pain, temperature up to 38,5°C, breathlessness. He had acute tonsillitis 2 weeks ago. He is in grave condition. The skin is pale. Heart borders are dilated, heart sounds are quiet. Above all heart area you can hear pericardium friction rub. Electrocardiogram: the descent of QRS voltage, the inversion T wave. The liver is enlarged by 3 cm. ESR - 4 mm/h, ASLO - 1260, C-reactive protein +++. Your diagnosis:

A. Rheumatic pancarditis
B. Rheumatic pericarditis
C. Rheumatic myocarditis
D. Rheumatic endocarditis
E. Septic endocarditis

3. A 19 y.o. girl admitted to the hospital complained of pain in the knee and fever of $38,6^0$C. She is ill for 2 weeks after acute tonsillitis. On exam, hyperemia and swelling of both knees, temperature is $37,4^0$C, Heart rate 94/min, BP 120/80 mm Hg, and heart borders are enlarged to the left; S1 is weak, diastolic murmur is present. CBC shows the following: Hb 120 g/L, WBC $9,8*10^9$/L, ESR 30 mm/h. ECG findings: the rhythm is regular, PQ = 0,24 sec. What is a causative agent of the disease?

A. Autoimmune disorder
B. Viral-bacterial association
C. Beta-hemolytic streptococci
D. Staphylococci
E. Ricchetsia

4. A 17 y.o. patient complains of acute pain in the knee joint and t^0- 38^0C. He was ill with upper respiratory infection 3 weeks ago. Objectively: deformation and swelling of the knee joints with skin hyperemia. Small movement causes an acute pain in the joints. Which diagnose is the most correct?

A. Rheumatoid arthritis
B. Systemic lupus erythematodes
C. Reactive polyarthritis
D. Infectious-allergic polyarthritis
E. Rheumatism, polyarthritis

5. A 25 year old patient had pharyngitis 2 weeks ago. Now he complains about body temperature rise up to 38°C, general weakness, dyspnea during walking, swelling and pain in the joints. Objectively: cyanosis of lips, weak rhythmic pulse 100 bpm. Left cardiac border deviates outwards from the mediaclavicular line by 1 cm. The first heart sound is weakened on the apex, auscultation revealed systolic mumur. What is the most probable aetiological factor that caused this pathological process?

A. β-haemolytic streptococcus
B. Staphylococcus
C. Pneumococcus
D. Virus
E. Fungi

6. After examination of a 35 y.o. patient the doctor made the following diagnosis: acute rheumatic fever, III degree of activity, combined mitral disease; heart failure I stage. According to abovementioned clinical conclusion the physician prescribed aspirin and penicillin. Find a mistake in doctor's prescription:

A. It was sufficient to prescribe only penicillin
B. Glucocorticoids (Prednisolone) were not prescribed
C. It was sufficient to prescribe only aspirin

D. It was essential to prescribe vitamins
E. Cytostatic was not prescribed

7. A patient 18 y.o. complaints of generalized weakness, rise of temperature up to 37.8C, palpitation, shortness of breath, pain in both knee joints. Two weeks ago the patient was ill with quinsy. Objectively: pale pink skin, pulse – 98 per minute, BP – 100/60 mmHg. Heart boarders +0.5 cm to the left side. I tone above the apex is weakened, mild systolic murmur. Choose the right doctor's prescription:

A. Direct at otolaryngologist's consultation
B. Examine and treat outpatient
C. Give the medical certificate and treat during 5 days
D. Direct at rheumatologist's consultation
E. Hospitalize and treat at the rheumatological department

List of recommended literature source:

Basic:

1. Contemporary Diagnosis and Management of Rheumatic Heart Disease: Implications for Closing the Gap. A Scientific Statement From the American Heart Association / R.K. Kumar, C.M.J. Antunes, A.Beaton et al. // Circulation. 2020;142:e337–e357. DOI: 10.1161/CIR.0000000000000921
2. The 2020 Australian guideline for prevention, diagnosis and management of acute rheumatic fever and rheumatic heart disease (3rd edition) / Ed. By B.Currie, A.Ralph // 2020 Menzies School of Health Research. 312 p.
3. Rheumatology: Principles and Practice. Ed.by S. Princeton. HAYLE MEDICAL, 2019. 248 p.
4. ABC of Rheumatology, 5th edition. Ed. by A.Adebajo and L.Dunkley. Hoboken, NJ : John Wiley & Sons, Inc., 2018. 209 p.
5. Rheumatology Secrets, 4th edition. Ed.by S.G. West, J. Kolfenbach. Elsevier, 2020. 744 p.

Additional:

1. Kelley and Firestein's Textbook of Rheumatology. 10th ed. / G.S. Firestein, I.B.McInnes et al. – Elsevier Health Sciences, 2017. - 1794 p.
2. Therapeutic Guidelines Rheumatology. – Therapeutic Guidelines Limited, 2017. – 335 p.

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European male of 23 years old.

Complaints: pressing pains in the heart area, a feeling of rapid heartbeat, weakness, fatigue, an increase in blood pressure up to 180/110 mm Hg, accompanied by headaches, an increase in body temperature up to 38.2 C.

Medical history: According to the patient, the condition worsened about 2 weeks ago, when, after a cold, pressing pains in the region of the heart, malaise, and other listed complaints appeared. On the ECG from – inversion of the T waves V3-V6, on the echocardiography – areas of hypokinesis were detected, EF = 65%, the deflection of the anterior valve of the MK 3 mm, separation of the pericardial sheets up to 7 mm. An additional examination was recommended. Analysis of TSH, T3, T4, ATPO – no pathology. Ultrasound of the thyroid gland – microfollicules, no significant pathology. Holter ECG monitoring – no significant deviations. At the present time patient went to the clinic in connection with the persisting complaints described above, examined by a cardiologist and rheumatologist, hospitalization is strongly recommended.

Life history: Grew and developed without lagging behind peers. Blood pressure has been increasing over the past 2 months, on the recommendation of a cardiologist, he takes nebivolol 5 mg / day, trimetazidine 35 mg 2 tab / day.

Allergic history is not burdened.

Hereditary history: parents suffered from cardiovascular diseases, father suffered 2 strokes.

Epidemiological anamnesis: Botkin's disease, tuberculosis, malaria, helminthiasis, candidiasis, blood transfusion for the last 3 months, the passage of the segments of the worms denies. He has not been abroad for the last 12 months.

Bad habits: smokes for about 7 years up to 1 pack per day. Drinks alcohol in moderation – up to 2 drinks per day.

Objective status: General condition of moderate severity. Hypersthenic constitution, satisfactory nutrition. Height 169 cm Weight - 96 kg.

The skin and visible mucous membranes are clean, pale pink.

The thyroid gland and peripheral lymph nodes are not enlarged.

Breathing over the lungs is vesicular, no wheezing. Percussion - clear pulmonary sound. Breath rate = 18 / min.

BP – 160/100 mm Hg symmetrical on both hands. Heart rhythm is regular, heart rate – 87 beats. in 1 min. Heart sounds are clear.

Tongue moist, coated with white bloom. The abdomen is soft and painless on palpation. The liver and spleen are not palpable.

The symptom of tapping over the projection of the kidneys is negative on both sides. No peripheral edema.

Diagnosis: Rheumatism, acute rheumatic fever, activity 2, rheumatic pericarditis, rheumatic myocarditis.

Arterial hypertension, stage 1, degree 1, risk 3.

Examination plan:

1. Cell blood count,
2. blood biochemistry,
3. acute-phase rheumatic tests,
4. coagulation test,
5. liver function tests,
6. kidney function tests,
7. lipid profile
8. urinalysis;
9. ECG,
10. Echocardiography,

11. Chest X-ray.

Treatment plan:

1. Bed rest, common diet.
2. Methylprednisolone 24 mg / day, orally, in morning, after meal
3. Amoxicillin / Clavulanic acid – 1000 / 200 mg – 3 times a day, i.v., every 8 hours
4. Omeprazole 20 mg 2 times a day, orally, before breakfast and before lunch
5. Meloxicam 1.5 ml i.m. in evening
6. Meldonium 5.0 ml i.v. one time a day
7. Quercetin 500 mg + 0,9% NaCl i.v. infusion one time a day
8. Nebivolol 5 mg / day, orally, in the morning, before meal

Appendix 2.

Tests of the initial level of knowledge of the KROK format

Topic 1. Rheumatic fever

1. A 28-year-old woman has been told she has rheumatic heart disease, specifically mitral stenosis. Which of the following murmurs is most likely present?

F. Pansystolic over all heart area
G. Diastolic rumble at apex of the heart
H. Early diastolic decrescendo at right upper sternal border
I. Holosystolic murmur at apex
J. Late-peaking systolic murmur at right upper sternal border

2. A 17 y.o. patient complains of shortness of breath, palpitation, general weakness, increasing of body temperature up to 37,1 – 37,3C, palpitation. Three weeks ago the man was diagnosed quinsy. On physical examination: heart sounds are arrhythmic, extrasystoles, mitral mild diastolic murmur. Choose the most likely causative agent:

F. Pneumococcus
G. Streptococcus viridans
H. Staphylococcus aureus
I. Streptococcus haemolyticus
J. Adenovirus

3. A 17 y.o. patient complains of dull pain in the heart area without irradiation, shortness of breath and palpitation with exercise. Objectively: temperature – 37.8C, heart rate - 96 per minute, soft systolic murmur at apex. ECG: interval PQ = 0.24 sec. In blood: ESR - 28 mm/h. Which investigation should be carried out to establish the etiology of the disease?

F. Blood cultures for sterility
G. Troponin T
H. Antibodies to streptococci
I. CRP
J. Fibrinogen

4. A 26 y.o. woman complaints of arthralgia, increase in body temperature, weakness, palpitation, pink rash on the skin in the form of rings. The abovementioned symptoms appeared 3 weeks ago after quinsy. Objectively: tachycardia, I tone above the heart apex is weak, mitral diastolic murmur. ECG: PQ = 0.24 sec. Antistreptolysin – O - 500 IU/ml. What methods of prevention can be assigned on an outpatient basis?

A. Take aspirin for concomitant diseases
B. Make injections of bitsillin-5 in spring and autumn
C. Make injections of bitsillin-5 before and after surgical operations
D. Take aspirin for a month in spring and autumn
E. Make injections of bitsillin-5 for 5 years

5. The third week after quinsy a 19 y.o. woman complaints of pain in the big joints of upper and lower limbs. Objectively: the affected joints are reddened and swollen; body temperature – 37.7C; pulse – 84 per minute. Heart boards +2 cm to the left side, I tone above the apex is weakened, systolic murmur. Hb – 126 g/l, L – $9.2x10^9$ /l, ESR – 47 mm/h. ECG: synus rhythm, PQ – 0.24 s. Choose the most likely causative agent:

A. Streptococcus aureus
B. Streptococcus haemoliticus
C. Herpes virus
D. CMV
E. Coxsackie virus

6. After examination of a 35 y.o. patient the doctor made the following diagnosis: acute rheumatic fever, III degree of activity, combined mitral disease; heart failure I stage. According to

abovementioned clinical conclusion the physician prescribed aspirin and penicillin. Find a mistake in doctor's prescription:

F. It was sufficient to prescribe only penicillin
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7. A patient 18 y.o. complaints of generalized weakness, rise of temperature up to 37.8C, palpitation, shortness of breath, pain in both knee joints. Two weeks ago the patient was ill with quinsy. Objectively: pale pink skin, pulse – 98 per minute, BP – 100/60 mmHg. Heart boarders +0.5 cm to the left side. I tone above the apex is weakened, mild systolic murmur. Choose the right doctor's prescription:

F. Direct at otolaryngologist's consultation
G. Examine and treat outpatient
H. Give the medical certificate and treat during 5 days
I. Direct at rheumatologist's consultation
J. Hospitalize and treat at the rheumatological department

8. Patient Z., 20 years old, in his childhood was diagnosed with chronic rheumatic heart disease: a combined mitral valvular disease with predominance of stenosis. Lately he's been noting heaviness in the right hypochondrium, edema of feet. Heart borders: right border on 1,5 cm outwards from the right edge of a sternum, the upper – II rib, the left – 1 cm. to the left from the left midclavicular line. Accent of II sound on pulmonary artery, systolic murmur above tricuspid valve. Liver + 4 cm, sensitive. Edema of ankles and feet. What complication has the patient developed?

A. Congestion in the pulmonary circulation.
B. Renal failure.
C. Right-sided heart failure.
D. Liver cirrhosis.
E. Left-sided heart failure.

9. A 18 y.o. male patient complains of pain in knee and ankle joints, temperature elevation to $39,5^0$C. He had a respiratory disease 1,5 week ago. On examination: temperature $38,5^0$C, swollen knee and ankle joints, pulse 106 bpm, rhythmic, BP 90/60 mmHg, heart borders without changes, heart sounds are weakened, soft diastolic apical murmur. What indicator is connected with possible etiology of the process?

A. 1-antitrypsine
B. Antistreptolysine-0
C. Creatinkinase
D. Rheumatic factor
E. Seromucoid

10. A female patient with rheumatism experiences diastolic thoracic wall tremor (diastolic thrill), accentuated S_1 at apex, there is diastolic murmur with presystolic intensification, opening snap, S_2 accent at pulmonary artery. What kind of heart disorder is observed?

A. Mitral valve insufficiency
B. Aortic valve insufficiency
C. Pulmonary artery stenosis
D. Mitral stenosis
E. Opened arterial duct

11. A 43 y.o. woman complains of shooting heart pain, dyspnea, irregularities in the heart activity, progressive fatigue during 3 weeks. She had acute respiratory disease a month ago. On examination: BP 120/80 mmHg, heart rate 98 bpm, heart boarders enlarged +1,5 cm to the left side, sounds are muffled, soft systolic murmur at apex and Botkin's area; periodically – premature complexes. Liver

isn't palpated, there are no edema. Blood test: WBC 6,7*10^9/L, ESR 21 mm/h. What is the most probable diagnosis?

A. Hypertrophic cardiomyopathy
B. Climacteric myocardiodystrophia
C. Ichemic heart disease, angina pectoris
D. Rheumatism, mitral insufficiency
E. Acute myocarditis

12. A 14 year old patient complains of chest pain, temperature up to 38,5ºC, breathlessness. He had acute tonsillitis 2 weeks ago. He is in grave condition. The skin is pale. Heart borders are dilated, heart sounds are quiet. Above all heart area you can hear pericardium friction rub. Electrocardiogram: the descent of QRS voltage, the inversion T wave. The liver is enlarged by 3 cm. ESR - 4 mm/h, ASLO - 1260, C-reactive protein +++. Your diagnosis:

A. Rheumatic pancarditis
B. Rheumatic pericarditis
C. Rheumatic myocarditis
D. Rheumatic endocarditis
E. Septic endocarditis

13. A 19 y.o. girl admitted to the hospital complained of pain in the knee and fever of $38,6^0$C. She is ill for 2 weeks after acute tonsillitis. On exam, hyperemia and swelling of both knees, temperature is $37,4^0$C, Heart rate 94/min, BP 120/80 mm Hg, and heart borders are enlarged to the left; S1 is weak, diastolic murmur is present. CBC shows the following: Hb 120 g/L, WBC $9,8*10^9$/L, ESR 30 mm/h. ECG findings: the rhythm is regular, PQ = 0,24 sec. What is a causative agent of the disease?

A. Autoimmune disorder
B. Viral-bacterial association
C. Beta-hemolytic streptococci
D. Staphylococci
E. Ricchetsia

14. A 17 y.o. patient complains of acute pain in the knee joint and t^0- 38^0C. He was ill with upper respiratory infection 3 weeks ago. Objectively: deformation and swelling of the knee joints with skin hyperemia. Small movement causes an acute pain in the joints. Which diagnose is the most correct?

A. Rheumatoid arthritis
B. Systemic lupus erythematodes
C. Reactive polyarthritis
D. Infectious-allergic polyarthritis
E. Rheumatism, polyarthritis

15. A 25 year old patient had pharyngitis 2 weeks ago. Now he complains about body temperature rise up to 38ºC, general weakness, dyspnea during walking, swelling and pain in the joints. Objectively: cyanosis of lips, weak rhythmic pulse 100 bpm. Left cardiac border deviates outwards from the mediaclavicular line by 1 cm. The first heart sound is weakened on the apex, auscultation revealed systolic mumur. What is the most probable aetiological factor that caused this pathological process?

A. β-haemolytic streptococcus
B. Staphylococcus
C. Pneumococcus
D. Virus
E. Fungi

Standard answers: 1-B, 2-D, 3-C, 4-E, 5-B, 6-B, 7-E, 8-C, 9-B, 10-D, 11-E, 12-A, 13-C, 14-E, 15-A.

Practical Lesson #3-4
Topic 2: Rheumatoid arthritis
Aim: To teach applicants to master the method of examination of patients with systemic connective tissue diseases with the selection of the main rheumatologic syndromes. To study probable etiological and predisposing factors, pathogenesis of rheumatoid arthritis, main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis.
Basic definitions:

№	Term	Definition
1.	Synovitis	Inflammation of the synovial membrane. This membrane lines joints that possess cavities, known as synovial joints. The condition is usually painful, particularly when the joint is moved. The joint usually swells due to synovial fluid collection. Synovitis is more commonly found in rheumatoid arthritis than in other forms of arthritis, and can thus serve as a distinguishing factor. Long term occurrence of synovitis can result in degeneration of the joint.
2.	Ulnar deviation	Is a hand deformity in which the swelling of the metacarpophalangeal joints (the big knuckles at the base of the fingers) causes the fingers to become displaced, tending towards the little finger. Its name comes from the displacement toward the ulna (as opposed to radial deviation, in which fingers are displaced toward the radius). Ulnar deviation is likely to be a characteristic of rheumatoid arthritis.
3.	Boutonniere deformity	Is a deformed position of the fingers or toes, in which the joint nearest the knuckle (the proximal interphalangeal joint, or PIP) is permanently bent toward the palm while the farthest joint (the distal interphalangeal joint, or DIP) is bent back away (PIP flexion with DIP hyperextension).
4.	Swan neck deformity	Is a deformed position of the finger, in which the joint closest to the fingertip is permanently bent toward the palm while the nearest joint to the palm is bent away from it (DIP flexion with PIP hyperextension).
5.	Rheumatoid nodule	Is a lump of tissue, or an area of swelling, that appear on the exterior of the skin usually around the olecranon (tip of the elbow) or the interphalangeal joints (finger knuckles), but can appear in other areas. There are four different types of rheumatoid nodules: subcutaneous, cardiac, pulmonary and central nervous systems nodules.

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that primarily involves the joints. RA causes damage mediated by cytokines, chemokines, and metalloproteases. Characteristically, peripheral joints (eg, wrists, metacarpophalangeal joints) are symmetrically inflamed, leading to progressive destruction of articular structures, usually accompanied by systemic symptoms. Diagnosis is based on specific clinical, laboratory, and imaging features. Treatment involves drugs, physical measures, and sometimes surgery. Disease-modifying antirheumatic drugs help control symptoms and slow disease progression.

Etiology

Although RA involves autoimmune reactions, the precise cause is unknown; many factors may contribute. A genetic predisposition has been identified and, in white populations, localized to a shared epitope in the HLA-DR β1 locus of class II histocompatibility antigens. Unknown or

unconfirmed environmental factors (eg, viral infections, cigarette smoking) are thought to play a role in triggering and maintaining joint inflammation.

Pathophysiology

Prominent immunologic abnormalities include immune complexes produced by synovial lining cells and in inflamed blood vessels. Plasma cells produce antibodies (eg, rheumatoid factor [RF], anticyclic citrullinated peptide antibody [anti-CCP]) that contribute to these complexes, but destructive arthritis can occur in their absence. Macrophages also migrate to diseased synovium in early disease; increased macrophage-derived lining cells are prominent along with vessel inflammation. Lymphocytes that infiltrate the synovial tissue are primarily CD4+ T cells. Macrophages and lymphocytes produce pro-inflammatory cytokines and chemokines (eg, tumor necrosis factors [TNF], granulocyte-macrophage colony-stimulating factor [GM-CSF], various ILs, interferon-γ) in the synovium. Release of inflammatory mediators probably contributes to the systemic and joint manifestations of RA.

In chronically affected joints, the normally thin synovium proliferates, thickens, and develops many villous folds. The synovial lining cells produce various materials, including collagenase and stromelysin, which contribute to cartilage destruction, and IL-1 and TNF-α, which stimulate cartilage destruction, osteoclast-mediated bone absorption, synovial inflammation, and prostaglandins (which potentiate inflammation). Fibrin deposition, fibrosis, and necrosis are also present. Hyperplastic synovial tissue (pannus) releases these inflammatory mediators, which erode cartilage, subchondral bone, articular capsule, and ligaments. PMNs on average make up about 60% of WBCs in the synovial fluid.

Rheumatoid nodules develop in about 30% of patients with RA. They are granulomas consisting of a central necrotic area surrounded by palisaded histiocytic macrophages, all enveloped by lymphocytes, plasma cells, and fibroblasts. Nodules and vasculitis can also develop in visceral organs.

Symptoms and Signs

Onset is usually insidious, often beginning with systemic and joint symptoms. Systemic symptoms include early morning stiffness of affected joints, generalized afternoon fatigue and malaise, anorexia, generalized weakness, and occasionally low-grade fever. Joint symptoms include pain, swelling, and stiffness.

The disease progresses most rapidly during the first 6 yr, particularly the first year; 80% of patients develop some permanent joint abnormalities within 10 yr. The course is unpredictable in individual patients.

Joint symptoms are characteristically symmetric. Typically, stiffness lasts > 60 min after rising in the morning but may occur after any prolonged inactivity (called gelling). Involved joints become tender, with erythema, warmth, swelling, and limitation of motion. The joints primarily involved include the following:

Wrists and the index (2nd) and middle (3rd) metacarpophalangeal joints (most commonly involved); Proximal interphalangeal joints; Metatarsophalangeal joints; Shoulders; Elbows; Hips; Knees; Ankles.

However, virtually any joint, except uncommonly the distal interphalangeal (DIP) joints, may be involved. The axial skeleton is rarely involved except for the upper cervical spine. Synovial thickening is detectable. Joints are often held in flexion to minimize pain, which results from joint capsular distention.

Fixed deformities, particularly flexion contractures, may develop rapidly; ulnar deviation of the fingers with an ulnar slippage of the extensor tendons off the metacarpophalangeal joints is typical, as are swan-neck and boutonnière deformities. Joint instability due to stretching of the joint capsule can also occur. Carpal tunnel syndrome can result from wrist synovitis compressing the median nerve. Popliteal (Baker) cysts can develop, causing calf swelling and tenderness suggestive of deep venous thrombosis.

Extra-articular manifestations: Subcutaneous rheumatoid nodules are not usually an early sign but eventually develop in up to 30% of patients, usually at sites of pressure and chronic

irritation (eg, the extensor surface of the forearm, metacarpophalangeal joints, occiput). Visceral nodules (eg, pulmonary nodules), usually asymptomatic, are common in severe RA.

Other extra-articular signs include vasculitis causing leg ulcers or mononeuritis multiplex, pleural or pericardial effusions, pulmonary infiltrates or fibrosis, pericarditis, myocarditis, lymphadenopathy, Felty syndrome, Sjögren syndrome, scleromalacia, and episcleritis. Involvement of the cervical spine can cause atlantoaxial subluxation and spinal cord compression; subluxation may worsen with extension of the neck (eg, during endotracheal intubation). Importantly, cervical spine instability is frequently asymptomatic.

Diagnosis

RA should be suspected in patients with polyarticular, symmetric arthritis, particularly if the wrists and 2nd and 3rd metacarpophalangeal joints are involved. Laboratory test results for RF, anti-CCP, and ESR or CRP. Other causes of symmetric polyarthritis, particularly hepatitis C, must be excluded. Patients should have a serum RF test, hand and wrist x-rays, and baseline x-rays of affected joints to document future erosive changes. In patients who have prominent lumbar symptoms, alternative diagnoses should be investigated.

RFs, antibodies to human γ-globulin, are present in about 70% of patients with RA. However, RF, often in low titers (levels can vary between laboratories), occurs in patients with other diseases, including other connective tissue diseases (eg, SLE), granulomatous diseases, chronic infections (eg, viral hepatitis, subacute bacterial endocarditis, TB), and cancers. Low RF titers can also occur in 3% of the general population and 20% of the elderly. An RF titer measured by latex agglutination of > 1:80 or a positive anti-CCP test supports the diagnosis of RA.

Anti-CCP antibodies have high specificity (90%) and sensitivity (about 77 to 86%) for RA and, like RF, predict a worse prognosis. RF and anti-CCP values do not fluctuate with disease activity.

X-rays show only soft-tissue swelling during the first months of disease. Subsequently, periarticular osteoporosis, joint space (articular cartilage) narrowing, and marginal erosions may become visible. Erosions often develop within the first year but may occur any time. MRI seems to be more sensitive and detects earlier articular inflammation and erosions. In addition, abnormal subchondral bone signals (eg, bone marrow lesions, bone marrow edema) around the knee suggest progressive disease.

If RA is diagnosed, additional tests help detect complications and unexpected abnormalities. CBC with differential should be obtained. A normochromic (or slightly hypochromic)-normocytic anemia occurs in 80%; Hb is usually > 10 g/dL. If Hb is ≤ 10 g/dL, superimposed iron deficiency or other causes of anemia should be considered. Neutropenia occurs in 1 to 2% of cases, often with splenomegaly (Felty syndrome). Acute-phase reactants (eg, thrombocytosis, elevated ESR, elevated C-reactive protein) reflect disease activity. A mild polyclonal hypergammaglobulinemia often occurs. ESR is elevated in 90% of patients with active disease.

Synovial fluid examination is necessary with any new-onset effusion to rule out other disorders and differentiate RA from other inflammatory arthritides (eg, septic and crystal-induced arthritis). In RA, during active joint inflammation, synovial fluid is turbid, yellow, and sterile, and usually has 10,000 to 50,000 WBCs/μL; PMNs typically predominate, but > 50% may be lymphocytes and other mononuclear cells. Crystals are absent.

Differential diagnosis: Many disorders can simulate RA:

- Crystal-induced arthritis
- Osteoarthritis
- SLE
- Sarcoidosis
- Reactive arthritis
- Psoriatic arthritis
- Ankylosing spondylitis
- Hepatitis C-related arthritis

RF can be nonspecific and is often present in several autoimmune diseases; the presence of anti-CCP antibodies is more specific for RA. For example, hepatitis C can be associated with an arthritis similar to RA clinically and that is RF-positive; however, anti-CCP is negative.

Some patients with crystal-induced arthritis may meet criteria for RA; however, synovial fluid examination should clarify the diagnosis. The presence of crystals makes RA unlikely. Joint involvement and subcutaneous nodules can result from gout, cholesterol, and amyloidosis as well as RA; aspiration or biopsy of the nodules may occasionally be needed.

SLE usually can be distinguished if there are skin lesions on light-exposed areas, hair loss, oral and nasal mucosal lesions, absence of joint erosions in even long-standing arthritis, joint fluid that often has < 2000 WBCs/μL (predominantly mononuclear cells), antibodies to double-stranded DNA, renal disease, and low serum complement levels. In contrast to RA, deformities in SLE are usually reducible because of the lack of erosions and bone or cartilage damage. Arthritis similar to RA can also occur in other rheumatic disorders (eg, polyarteritis, systemic sclerosis, dermatomyositis, or polymyositis) or there can be features of more than one disease, which suggests an overlap syndrome or mixed connective tissue disease.

Sarcoidosis, Whipple disease, multicentric reticulohistiocytosis, and other systemic diseases may involve joints; other clinical features and tissue biopsy sometimes help differentiate these conditions. Acute rheumatic fever has a migratory pattern of joint involvement and evidence of antecedent streptococcal infection (culture or changing antistreptolysin O titer); in contrast, RA has an additive arthritis.

Reactive arthritis can be differentiated by antecedent GI or GU symptoms; asymmetric involvement and pain at the Achilles insertion of the heel, sacroiliac joints, and large joints of the leg; conjunctivitis; iritis; painless buccal ulcers; balanitis circinata; or keratoderma blennorrhagicum on the soles and elsewhere.

Psoriatic arthritis tends to be asymmetric and is not usually associated with RF, but differentiation may be difficult in the absence of nail or skin lesions. DIP joint involvement and severely mutilating arthritis (arthritis mutilans) is strongly suggestive, as is the presence of a diffusely swollen (sausage) digit. Ankylosing spondylitis may be differentiated by spinal and axial joint involvement, absence of subcutaneous nodules, and a negative RF test.

Osteoarthritis (OA) can be differentiated by the joints involved; the absence of rheumatoid nodules, systemic manifestations, or significant amounts of RF; and synovial fluid WBC counts < 2000/μL. Osteoarthritis of the hands most typically involves the DIP joints, bases of the thumbs, and proximal interphalangeal joints. RA does not affect the DIP joints.

Prognosis

RA decreases life expectancy by 3 to 7 yr, with heart disease, infection, and GI bleeding accounting for most excess mortality; drug treatment, cancer, as well as the underlying disease may be responsible.

At least 10% of patients are eventually severely disabled despite full treatment. Whites and women have a poorer prognosis, as do patients with subcutaneous nodules, advanced age at disease onset, inflammation in ≥ 20 joints, early erosions, cigarette smoking, high ESR, and high levels of RF or anti-CCP.

Treatment

Treatment involves a balance of rest and exercise, adequate nutrition, physical measures, drugs, and sometimes surgery.

Rest and nutrition: Complete bed rest is rarely indicated, even for a short time; however, a program including judicious rest should be encouraged. An ordinary nutritious diet is appropriate. Rarely, patients have food-associated exacerbations; no specific foods have reproducibly been shown to exacerbate RA. Food and diet quackery is common and should be discouraged. Substituting ω-3 fatty acids (in fish oils) for dietary ω-6 fatty acids (in meats) partially relieves symptoms in some patients by transiently decreasing production of inflammatory prostaglandins.

Physical measures: Joint splinting reduces local inflammation and may relieve severe symptoms. Cold may be applied to reduce pain from temporary worsening in one joint. Orthopedic

or athletic shoes with good heel and arch support are frequently helpful; metatarsal supports placed posteriorly (proximal) to painful metatarsophalangeal joints decrease the pain of weight bearing. Molded shoes may be needed for severe deformities. Occupational therapy and self-help devices enable many patients with debilitating RA to perform activities of daily living.

Exercise should proceed as tolerated. During acute inflammation, passive range-of-motion exercise helps prevent flexion contractures. Heat therapy can be helpful. Range-of-motion exercises done in warm water are helpful because heat improves muscle function by reducing stiffness and muscle spasm. However, contractures can be prevented and muscle strength can be restored more successfully after inflammation begins to subside; active exercise (including walking and specific exercises for involved joints) to restore muscle mass and preserve range of joint motion should not be fatiguing. Flexion contractures may require intensive exercise, casting, or immobilization (eg, splinting) in progressively more stretched-open positions. Paraffin baths can warm digits and facilitate finger exercise. Massage by trained therapists, traction, and deep heat treatment with diathermy or ultrasonography may be useful adjunctive therapies to anti-inflammatory drugs.

Surgery: Surgery must always be considered in terms of the total disease and patient expectations. For example, deformed hands and arms limit crutch use during rehabilitation; seriously affected knees and feet limit benefit from hip surgery. Reasonable objectives for each patient must be determined, and function must be considered. Surgery may be done while the disease is active.

Arthroplasty with prosthetic joint replacement is indicated if damage severely limits function; total hip and knee replacements are most consistently successful. Prosthetic hips and knees cannot tolerate vigorous activity (eg, competitive athletics). Excision of subluxed painful metatarsophalangeal joints may greatly aid walking. Thumb fusions may provide stability for pinch. Neck fusion may be needed for C1-2 subluxation with severe pain or potential for spinal cord compression. Arthroscopic or open synovectomy can relieve joint inflammation but only temporarily unless disease activity can be controlled.

Drugs for RA

The goal is to reduce inflammation as a means of preventing erosions, progressive deformity, and loss of joint function. Disease-modifying antirheumatic drugs (DMARDs) are used early, often in combination. Other drug classes, including biologic agents, TNF-α antagonists, and IL-1 receptor antagonists, seem to slow the progression of RA. NSAIDs are of some help for the pain of RA but do not prevent erosions or disease progression and thus should be used only as adjunctive therapy. Low-dose systemic corticosteroids (prednisone < 10 mg once/day) may be added to control severe polyarticular symptoms, usually with the objective of replacement with a DMARD. Intra-articular depot corticosteroids can control severe monarticular or even oligoarticular symptoms. The optimal combinations of drugs are not yet clear. However, some data suggest that certain combinations of drugs from different classes (eg, methotrexate plus other DMARDs, a rapidly tapered corticosteroid plus a DMARD, methotrexate plus a TNF-α antagonist or an IL-1 receptor antagonist, a TNF-α antagonist or an IL-1 receptor antagonist plus a DMARD) are more effective than using DMARDs alone sequentially or in combination. In general, biologic agents (eg, TNF-α and IL-1 receptor antagonists) are not given in combination with each other due to increased frequency of infections. An example of initial therapy is methotrexate 7.5 mg po once/wk (with folic acid 1 mg po once/day). If tolerated and not adequate, the dose of methotrexate is increased after 3- to 5-wk intervals to a maximum of 20 mg po once/wk. If response is not adequate, a biologic agent is added.

NSAIDs: Aspirin is no longer used for RA, as effective doses are often toxic. Only one NSAID should be given at a time, although patients may also take aspirin at ≤ 325 mg/day for its antiplatelet cardioprotective effect. Because the maximal response for NSAIDs can take up to 2 wk, doses should be increased no more frequently than this. Doses of drugs with flexible dosing can be increased until response is maximal or maximum dosage is reached. All NSAIDs treat the symptoms of RA and decrease inflammation but do not alter the course of the disease; thus, they are only used adjunctively.

NSAIDs inhibit cyclooxygenase (COX) enzymes and thus decrease production of prostaglandins. Some prostaglandins under COX-1 control have important effects in many parts of the body (ie, they protect gastric mucosa and inhibit platelet adhesiveness). Other prostaglandins are induced by inflammation and are produced by COX-2. Selective COX-2 inhibitors, also called coxibs (eg, celecoxib), seem to have efficacy comparable to nonselective NSAIDs and are slightly less likely to cause GI toxicity; however, they are not less likely to cause renal toxicity.

NSAIDs other than coxibs should be avoided in patients with previous peptic ulcer disease or dyspepsia. Other possible adverse effects of all NSAIDs include headache, confusion and other CNS symptoms, increased BP, worsening of hypertension, edema, and decreased platelet function. NSAIDs increase cardiovascular risk. Creatinine levels can rise reversibly because of inhibited renal prostaglandins; less frequently, interstitial nephritis can occur. Patients with urticaria, rhinitis, or asthma caused by aspirin can have the same problems with these other NSAIDs.

Traditional disease-modifying antirheumatic drugs (DMARDs): DMARDs seem to slow the progression of RA and are indicated for nearly all patients with RA. They differ from each other chemically and pharmacologically. Many take weeks or months to have an effect. About two thirds of patients improve overall, and complete remissions are becoming more common. Many DMARDs result in evidence of decreased damage on imaging studies, presumably reflecting decreased disease activity. Patients should be fully apprised of the risks of DMARDs and monitored closely for evidence of toxicity.

Combinations of DMARDs may be more effective than single drugs. For example, hydroxychloroquine, sulfasalazine, and methotrexate together are more effective than methotrexate alone or the other two together. Also, combining a DMARD with another drug, such as methotrexate plus a TNF-α antagonist or an IL-1 receptor antagonist or a rapidly tapered corticosteroid, may be more effective than using DMARDs alone.

Methotrexate is a folate antagonist with immunosuppressive effects at high dose. It is anti-inflammatory at doses used in RA. It is very effective and has a relatively rapid onset (clinical benefit often within 3 to 4 wk). Methotrexate should be used with caution, if at all, in patients with hepatic dysfunction or renal failure. Alcohol should be avoided. Supplemental folate, 1 mg po once/day, reduces the likelihood of adverse effects. CBC, AST, ALT, and albumin and creatinine level should be determined about every 8 wk. Rarely, a liver biopsy is needed if liver function test findings are persistently twice the upper limit of normal or more and the patient needs to continue to use methotrexate. Severe relapses of arthritis can occur after withdrawal of methotrexate. Paradoxically, rheumatoid nodules may enlarge with methotrexate therapy.

Hydroxychloroquine can also control symptoms of mild RA. Funduscopic examination should be done and visual fields should be assessed before and every 12 month during treatment. The drug should be stopped if no improvement occurs after 9 month.

Sulfasalazine can alleviate symptoms and slow development of joint damage. It is usually given as enteric-coated tablets. Benefit should occur within 3 mo. Enteric coating or dose reduction may increase tolerability. Because neutropenia may occur early, CBCs should be obtained after 1 to 2 wk and then about every 12 wk during therapy. AST and ALT should be obtained at about 6-mo intervals and whenever the dose is increased.

Leflunomide interferes with an enzyme involved with pyrimidine metabolism. It is about as effective as methotrexate but is less likely to suppress bone marrow, cause abnormal liver function, or cause pneumonitis. Alopecia and diarrhea are fairly common at the onset of therapy but may resolve with continuation of therapy.

Parenteral gold compounds are not commonly used anymore.

Corticosteroids: Systemic corticosteroids decrease inflammation and other symptoms more rapidly and to a greater degree than other drugs. They also seem to slow bone erosion. However, they do not prevent joint destruction, and their clinical benefit often diminishes with time. Furthermore, rebound often follows the withdrawal of corticosteroids in active disease. Because of their long-term adverse effects, many doctors recommend that corticosteroids are given to maintain function only until another DMARD has taken effect.

Corticosteroids may be used for severe joint or systemic manifestations of RA (eg, vasculitis, pleurisy, pericarditis). Relative contraindications include peptic ulcer disease, hypertension, untreated infections, diabetes mellitus, and glaucoma. The risk of latent TB should be considered before corticosteroid therapy is begun.

Intra-articular injections of depot corticosteroids may temporarily help control pain and swelling in particularly painful joints. Triamcinolone hexacetonide may suppress inflammation for the longest time. Triamcinolone acetonide and methylprednisolone acetate are also effective. No single joint should be injected with a corticosteroid more than 3 to 4 times a year, as too-frequent injections may accelerate joint destruction (although there are no specific data from humans to support this effect). Because injectable corticosteroid esters are crystalline, local inflammation transiently increases within a few hours in < 2% of patients receiving injections. Although infection occurs in only < 1:40,000 patients, it must be considered if pain occurs > 24 h after injection.

Immunomodulatory, cytotoxic, and immunosuppressive drugs: Treatment with azathioprine or cyclosporine (an immunomodulatory drug) provides efficacy similar to DMARDs. However, these drugs are more toxic. Thus, they are used only for patients in whom treatment with DMARDs has failed or to decrease the need for corticosteroids. They are used infrequently unless there are extra-articular complications. For maintenance therapy with azathioprine, the lowest effective dose should be used.

Low-dose cyclosporine may be effective alone or when combined with methotrexate. It may be less toxic than azathioprine.

Cyclophosphamide is no longer recommended due to its toxicity.

Biologic agents: Biologic response modifiers other than TNF-α antagonists can be used to target B cells or T cells. These agents are typically not combined with each other.

Rituximab is an anti-CD 20 antibody that depletes B cells. It can be used in refractory patients. Response is often delayed but may last 6 mo. The course can be repeated in 6 mo. Mild adverse effects are common, and analgesia, corticosteroids, diphenhydramine, or a combination may need to be given concomitantly. Rituximab is usually restricted to patients who have not improved after using a TNF inhibitor and methotrexate. Rituximab therapy has been associated with progressive multifocal leukoencephalopathy, mucocutaneous reactions, and hepatitis B reactivation.

Abatacept, a soluble fusion cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) Ig, is indicated for patients with RA with an inadequate response to other DMARDs.

Other agents: Anakinra is a recombinant IL-1 receptor antagonist. IL-1 is heavily involved in the pathogenesis of RA. Infection and leukopenia can be problems.

TNF-α antagonists (eg, adalimumab, etanercept, golimumab, certolizumab pegol, tocilizumab, and infliximab) reduce the progression of erosions and reduce the number of new erosions. Although not all patients respond, many have a prompt, dramatic feeling of well being, sometimes with the first injection. Inflammation is often dramatically reduced.

Tocilizumab blocks the effect of IL- 6 and has clinical efficacy in patients who have responded incompletely to other biologic agents.

Although there are some differences among agents, the most serious problem is infection, particularly with reactivated TB. Patients should be screened for TB with PPD or an interferon-gamma release assay. Other serious infections can occur, including sepsis, invasive fungal infections, and infections due to other opportunistic organisms. It is not clear whether risk of lymphomas or other cancers is increased. Recent information suggests safety during pregnancy. TNF-α antagonists should probably be stopped before major surgery. Etanercept, infliximab, and adalimumab can and probably should be used with methotrexate. High-dose infliximab should not be used in patients with severe heart failure.

Equipment: training room, negatoscope, computer, X-ray machine.

Lesson duration: 4 hours

Plan

1. Organizational moment (greetings, checking the audience, the message of the topic, the purpose of the lesson, the motivation of applicants to study the topic).

2. Control of basic knowledge (initial survey with tests of the STEP 2 format – attached, check of workbooks on the topic):

2.1. Requirements for theoretical readiness of applicants to perform practical classes.

Knowledge requirements:

- Definition of rheumatoid arthritis
- Current views on the etiology and pathogenesis of rheumatoid arthritis
- Classification of rheumatoid arthritis
- Clinical presentation of rheumatoid arthritis
- Diagnostic of rheumatoid arthritis
- Differential diagnostic
- Complications of rheumatoid arthritis
- Treatment of rheumatoid arthritis
- Prognosis for patients with rheumatoid arthritis

List of didactic units:

- to collect in detail the anamnesis of the disease;
- to conduct a physical examination of the patient, to identify and assess changes in his condition;
- make a plan for additional examination, evaluate its results;
- formulate and substantiate a preliminary and clinical diagnosis of rheumatoid arthritis, taking into account the severity of disorders according to the classification, comprehensive assessment of patients;
- assessment of possible complications of rheumatoid arthritis;
- evaluation of the results of general clinical examination, laboratory analysis of blood, data of X-rays, CTs, MRIs, ultrasound, etc.

2.2. Questions (tests, tasks, clinical cases) to test basic knowledge on the topic of the lesson:

The tests for self-control with standard answers.

1. In the development of the inflammation processes glucocorticoids reduce the level of certain most important active enzyme. It results also in the reducing of the synthesis of prostaglandins and leucotrienes which have a key role in the development of inflammation processes. What is the exact name of this enzyme?

A. Phospholipase A2
B. Arachidonic acid
C. Lipoxygenase
D. Cyclooxygenase-1
E. Cyclooxygenase-2

2. A patient has an over a year-old history of fast progressive rheumatoid arthritis. X-raying confirms presence of marginal erosions. What basic drug would be the most appropriate in this case?

A. Prednisolone
B. Chloroquine
C. Methotrexate
D. Diclofenac sodium
E. Aspirin

3. A 35-year-old patient complains about pain and morning stiffness of hand joints and temporomandibular joints that lasts over 30 minutes. She has had these symptoms for 2 years. Objectively: edema of proximal interphalangeal digital joints and limited motions of joints. What examination should be administered?

A. Proteinogram

B. Complete blood count
C. Rose-Waaler's reaction
D. Immunnogram
E. Roentgenography of hands

4. A 31 y.o. woman has complained for 3 years of pain and swelling of radiocarpal and metacarpophalangeal articulations, morning stiffness that lasts up to 1,5 hours. Two weeks ago she felt pain, swelling and reddening of knee joints, body temperature raised up to $37,5^0$C. Examination of her internal organs revealed no pathologic changes. Her diagnosis was rheumatoid arthritis. What changes in X-ray pictures of her joints are the most probable?

A. Constriction of joint space, usura
B. Constriction of joint space, subchondral osteosclerosis
C. Cysts in subchondral bone
D. Multiple marginal osteophytes
E. Epiphysis osteolysis

5. A 38 year old female patient complains about body stiffness in the morning, especially in the articulations of her upper and lower limbs, that disappears 30-60 minutes later after active movements. She has also arthritis of metacarpophalangeal and proximal phalangeal articulations, subfebrile temperature. ESR- 45 mm/h. Roentgenography revealed osteoporosis and erosion of articular surface of small hand and foot articulations. What is the most probable diagnosis?

A. Psoriatic arthropathy
B. Rheumatoid arthritis
C. Osteoarthrosis deformans
D. Systemic lupus erythematosus
E. Reactive polyarthritis

Clinical case with standards answers:

Case 1. 60 years old female patient complained of stiffness in small joints of both hands, duration for 2-3 hours, which accompanied by pain, swelling of the these joints, weight loss, decreased appetite, sweating, subfebrile body temperature in the evening. The skin over the joints hyperemic, hot to the touch. Additional research methods: CBC - Hb - 122 g / l, Er 4,3 x 10^{12} / l L. 12 x 10^9/л, e – 2, b- 5, s – 75, lym – 12, m – 6, ESR - 35 mm / h, RF (+), alpha 2 globulin - 14%, CRP + +, on X-rays of hands osteoporosis, subchondral destruction.

1. Primary clinical diagnosis.
2. Plan of additional investigation
3. Treatment.

Answering standards

1. Rheumatoid arthritis (polyarthritis), the active phase II degree of activity, seropositive, Ro II stage.
2. Radiography of affected joints. The general analysis of blood biochemical parameters (rheumatoid factor, alpha 2 globulin, CRP, seromucoid, ASLO). MRI or Ultrasound of affected joints.
3. Main Program: Systemic therapy (basic – methotrexate), anti-inflammatory (NSAIDs and glucocorticoids), side effect prophylaxis (folic acid). Physiotherapy. Massage. Mechanical and occupational therapy.

Case 2. Patient with rheumatoid arthritis in history began to complain of retrosternal pain, shortness of breath on exertion, swelling of lower extremities in the evening. On ECG - a decrease in voltage of all waves.

What is the main complication of the disease have developed in a patient?

Answering standard

Pericarditis.

3. Formation of professional skills, abilities (mastering the skills of curation, determining the treatment regimen):

Recommendations for tasks: (professional algorithms):

Work at the patient's bedside (according to the algorithm of communication between applicants and patients).

When examining patients, students must follow the following communication algorithms:

Collection of complaints and anamnesis in patients with internal diseases

1. Friendly facial expression, smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Collection of complaints and medical history of the patient.
5. Explanation of survey results.
6. Explanation of actions (hospitalization, conducting certain examinations) that are planned to be performed in the future.
7. End the conversation.

Physical methods of examination of patients with internal diseases

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Explain to the patient which examination will be performed and obtain his consent.
6. Warning about the possibility of unpleasant feelings during the examination.
7. Preparation for the examination (clean warm hands, trimmed nails, warm stethoscope, if necessary – use a screen).
8. Conducting an examination (demonstration of clinical skills).
9. Explanation of survey results.
10. End the conversation.

Reporting the results of the examination to patients with internal diseases.

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the results of a particular examination.
5. Involve the patient in the interview (compare the results of this examination with previous results, find out if they understand your explanations).
6. End the conversation.

Planning and forecasting the results of conservative treatment:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the need for prescribed treatment.
5. Involvement of the patient (emphasis on the peculiarities of the drugs, duration of administration, possible side effects; find out whether the patient understands your explanations).
6. End the conversation.

Treatment prognosis message:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the expected results of the prescribed treatment.
5. Involve the patient in the conversation (emphasis on the importance of continuous treatment, adherence to the prescribed treatment regimen, finding out whether your explanations are clear to the patient).
6. End the conversation.

Work 1.

1. Collection of complaints, anamnesis, examination of a patient with acute rheumatic fever.
2. Detection of clinical symptoms.
3. Grouping of symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data (clinical analysis of blood, urine, biochemical analysis of blood, chest X-ray or chest CT-scan, X-ray of joints or MRI or ultrasound of joints, ECG, echocardiography, etc.).
6. Carrying out of the differential diagnosis with other arthritis.
7. Formulation of the clinical diagnosis.
8. Determining the degree of disability.

Work 2.

Appointment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the cathedral library with thematic literature.

The student fills in the protocol of examination of the patient in writing. An example of the initial examination of the patient is attached.

Control materials for the final stage of the lesson:

Tasks for self-control with answers.

1. In the development of the inflammation processes glucocorticoids reduce the level of certain most important active enzyme. It results also in the reducing of the synthesis of prostaglandins and leucotrienes which have a key role in the development of inflammation processes. What is the exact name of this enzyme?

A. Phospholipase A2
B. Arachidonic acid
C. Lipoxygenase
D. Cyclooxygenase – 1
E. Cyclooxygenase – 2

2. A patient has an over a year-old history of fast progressive rheumatoid arthritis. X-raying confirms presence of marginal erosions. What basic drug would be the most appropriate in this case?

A. Prednisolone
B. Chloroquine
C. Methotrexate
D. Diclofenac sodium

E. Aspirin

3. A 35-year-old patient complains about pain and morning stiffness of hand joints and temporomandibular joints that lasts over 30 minutes. She has had these symptoms for 2 years. Objectively: edema of proximal interphalangeal digital joints and limited motions of joints. What examination should be administered?

A. Proteinogram
B. Complete blood count
C. Rose-Waaler's reaction
D. Immunogram
E. Hands X-ray

4. A 31 y.o. woman has complained for 3 years of pain and swelling of radiocarpal and metacarpophalangeal articulations, morning stiffness that lasts up to 1,5 hours. Two weeks ago she felt pain, swelling and reddening of knee joints, body temperature raised up to $37,5^0$C. Examination of her internal organs revealed no pathologic changes. Her diagnosis was rheumatoid arthritis. What changes in X-ray pictures of her joints are the most probable?

A. Constriction of joint space, usura
B. Constriction of joint space, subchondral osteosclerosis
C. Cysts in subchondral bone
D. Multiple marginal osteophytes
E. Epiphysis osteolysis

5. A 38 year old female patient complains about body stiffness in the morning, especially in the articulations of her upper and lower limbs, that disappears 30-60 minutes later after active movements. She has also arthritis of metacarpophalangeal and proximal phalangeal articulations, subfebrile temperature. ESR- 45 mm/h. Roentgenography revealed osteoporosis and erosion of articular surface of small hand and foot articulations. What is the most probable diagnosis?

A. Psoriatic arthropathy
B. Rheumatoid arthritis
C. Osteoarthritis
D. Systemic lupus erythematosus
E. Reactive polyarthritis

List of recommended literature source:

Basic:

1. 2021 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis / L. Fraenkel, J.M. Bathon, B.R. England et al. // Arthritis Care & Research Vol. 73, No. 7, July 2021, pp 924–939
2. EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis / G.Nagy, N.M.T.Roodenrijs, P.M.J.Welsing et al. // Ann. Rheum. Dis. Published Online First: 18 August 2021. doi:10.1136/annrheumdis-2021-220973
3. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Smolen JS, Landewé R, Bijlsma J, et al. Ann Rheum Dis 2017;76:960–977.
4. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Smolen JS, Landewé RBM, Bijlsma JWJ, et al. Ann Rheum Dis 2020;79:685–699.

Additional:

1. Rheumatology: Principles and Practice. Ed.by S. Princeton. HAYLE MEDICAL, 2019. 248 p.
2. ABC of Rheumatology, 5th edition. Ed. by A.Adebajo and L.Dunkley. Hoboken, NJ : John Wiley & Sons, Inc., 2018. 209 p.
3. Rheumatology Secrets, 4th edition. Ed.by S.G. West, J. Kolfenbach. Elsevier, 2020. 744 p.

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European female of 38 years old.

Complaints: pain in small joints of the hands, wrist, elbow, shoulder, knee, ankle, foot joints, hip joints, lumbar spine, cervical spine, joint swelling, morning stiffness about 1-1.5 hours (up to 3 hours), impaired motor functions of the joints, dyspnea of a mixed nature, with minimal exertion and at rest, periodic edema of the lower extremities, weakness, fatigue, pain in the left hypochondrium, headaches.

Medical history: Considers herself ill for about 20 years, when swelling and moderate pain first appeared in the third proximal interphalangeal joint, then other joints began to be involved in the process. One year later she was diagnosed with rheumatoid arthritis, underwent inpatient treatment at the Odessa Regional Clinical Hospital, and was treated with NSAIDs. The disease progressed. 7 years later the patient underwent endoprosthetics of the right hip joint, one more year later - the right knee joint, and one more year later – the left knee joint. She underwent inpatient treatment several times, constantly taking methylprednisolone, the dosage is currently 8 mg / day. The present worsening of the condition is noted within a month, when all the symptoms worsened, a severe headache began to disturb. Hospitalization in the internal medicine department with intensive care beds has been agreed.

Life history: Material and living conditions are satisfactory. At age 6 suffered from viral hepatitis A. At age 7 – appendectomy. Frequent tonsillitis (4 times per year), in 20 years age – cryodestruction of the tonsils. Chronic pyelonephritis for more than 3 years (undergoing hospital treatment). Tuberculosis, venereal disease, denies. According to the patient, an allergic reaction to the basic therapy of RA: methotrexate, plaquenil, leflunomide, sulfasalazine, delagil, as well as from the words of the patient to warfarin, rheopolyglucin. There were no occupational hazards. Hereditary history is not burdened. Does not smoke, does not abuse alcohol. Gynecological history: there were no pregnancies, no births. She has not been in contact with infectious patients in the last 3 days. She has not left the country for the last 3 years.

Objective status: The general condition of the patient is of moderate severity, clear consciousness. The physique is correct.

The physiological curves of the back are smoothed out. The position in bed is active.

The skin and visible mucous membranes are clear, bluish-purple color of the skin over the proximal interphalangeal joints of the right hand. Subcutaneous fat is developed evenly, with some excess in the abdomen.

Nutrition normal. Body mass index = 21,8 kg/m2.

Above the lungs percussion: over the entire surface of the lungs, a clear percussion sound with a box shade.

Auscultation over the lungs: hard breathing, some weakened over the lower parts of lungs on both sides. Breath rate = 22 / min., SpO2 = 99%.

The boundaries of relative cardiac dullness are expanded mainly to the left. Heart sounds are rhythmic, muffled over all points of auscultation. BP 105/70 mm Hg, heart rate 92 / min.

The abdomen is rounded, soft, painful on palpation in the epigastrium and left hypochondrium. The percussion borders of the spleen are enlarged. Sections of the intestine of normal palpation properties. The liver is at the edge of the ribs, sensitive to palpation.

No peripheral edema. Pasternatsky's symptom is weakly positive on the right side.

Defiguration and formation of flexion contractures of the joints of the hands, elbow joints. Fusiform thickening of the proximal interphalangeal joints. Swelling of the joints, pain on palpation and papillary movements. Decreased muscle strength in the hands.

Diagnosis:

Rheumatoid arthritis, polyarthritis of the joints of the hands and wrist, elbow, neck, shoulder, continuously recurrent course, seronegative, activity III, with visceral manifestations

(interstitial lung disease, stage II, mild anemia, splenomegaly). Condition after knee and hip arthroplasty.

Cushing's syndrome (drug-related).

Widespread osteochondrosis of the spine with a predominant lesion of the cervical spine with pronounced cephalgic syndrome.

Examination plan:

1. Cell blood count,
2. Blood biochemistry,
3. Acute-phase rheumatic tests,
4. Coagulation test,
5. Liver function tests,
6. Kidney function tests,
7. Lipid profile
8. Urinalysis;
9. ECG,
10. Echocardiography,
11. Chest X-ray.
12. Densitometry

Treatment plan:

1. Bed rest, common diet.
2. Methylprednisolone 1000 mg / day, i.v. infusion once a day, 3 days
3. Methylprednisolone 8 mg / day, orally, in morning, after meal
4. Paracetamol 1000 mg i.v. infusion
5. Azathioprine 50 mg orally twice a day
6. Pantoprazole 40 mg i.v.
7. Torasemide 20 mg i.v.

Appendix 2.

Tests of the initial level of knowledge of the KROK format

Topic 2. Rheumatoid arthritis

1. A patient 45 years old, complains of pains, edema and constraint of symmetric metacarpophalangeal and proximal interphalangeal joints, subfertility, moderate constraint about 1 hour. The beginning of what disease does the patient have?

A. Osteoarthritis.
B. Gout.
C. Raynaud's syndrome.
D. Rheumatoid arthritis
E. Ankylosing spondylitis.

2. Atypical for the RA (joints of exclusion) damage:

A. Proximal interphalangeal joints
B. Distal interphalangeal joints
C. 2nd and 3rd metacarpophalangeal joints
D. Wrist joints
E. Elbow

3. A 35-year-old patient complains about pain and morning stiffness of hand joints and temporomandibular joints that lasts over 30 minutes. She has had these symptoms for 2 years. Objectively: edema of proximal interphalangeal digital joints and limited motions of joints. What examination should be administered?

A. X-ray of hand's joints
B. Complete blood count
C. Rose-Waaler reaction
D. Immunogram
E. Proteinogram

4. In the X-ray of the damaged joints are not found:

A. Epiphyseal osteoporosis
B. Marginal bone erosions
C. The narrowing of the joint gaps
D. Cystoid cavities in the epiphysis
E. Joint ankylosis

5. Patient K., 32 years old, complaining of pain and morning stiffness in the II and III proximal interphalangeal and metacarpophalangeal joints lasting more than 3 hours. Objectively - smoothed contours of the joints, palpation of the joints is painful, active and passive movements are limited. DAS4 - 2,38. RF titer in serum increased. Optimal starting drug therapy will be the base:

A. Metotrexate
B. D-penicillamine
C. Cyclosporin A
D. Sulfasalazine
E. Azathyoprine

6. A 34 year old woman fell ill 3 months ago after cold exposure. She complained of pain in her hand and knee joints, morning stiffness and fever up to 38ºC. Interphalangeal, metacarpophalangeal and knee joints are swollen, hot, with reduced ranges of motions; ESR of 45 mm/h, CRP (+++), Vaaler-Rouse test of 1:128. What group of medicines would you recommend the patient?

A. Nonsteroidal anti-inflammatory drugs +
B. Cephalosporines
C. Tetracyclines
D. Sulfonamides

E. Fluorchinolones

7. A 30 y.o. female with rheumatoid arthritis of five years duration complains of pain in the first three fingers of her right hand over past 6 weeks. The pain seems especially severe at night often awakening her from sleep.The most likelly cause is?

A. Carpal tunnel syndrome

B. Atlanto-axial sublaxation of cervical spine

C. Sensory peripheral neuropathy

D. Rheumatoid vasculitis

E. Rheumatoid arthritis without complication

8. A patient has an over a year-old history of fast progressive rheumatoid arthritis. X-raying confirms presence of marginal erosions. What basic drug would be the most appropriate in this case?

A. Methotrexate

B. Chloroquine

C. Prednisolone

D. Diclofenac sodium

E. Aspirin

9. In the treatment of monotherapy-resistant cases, methotrexate better to combine with:

A. GS (Prednisolone)

B. NSAIDs (diclofenac)

C. 4-aminoquinoline derivatives (Plaquenil)

D. Sulfasalazine

E. Biological agents (Infliximab)

10. The criteria of clinical remission of RA is the level of ESR:

A. 30-20 mm / h

B. 15-10 mm / h

C. 10-5 mm / h

D. 20-15 mm / h

E. 40-30 mm / h

Practical Lessons # 5-6

Topic 3: Systemic connective tissue diseases. Systemic lupus erythematosus (SLE). Systemic scleroderma.

Aim: To teach students to master the method of examination of patients with SLE with the selection of the main rheumatologic syndromes. To study probable etiological and predisposing factors, pathogenesis of acute SLE, main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis, methods of primary and secondary prophylaxis.

Basic definitions:

№	Term	Definition
1.	Carditis	Inflammation of the heart. It is usually studied and treated by specifying it as: *pericarditis* – is the inflammation of the pericardium; *myocarditis* – is the inflammation of the heart muscle; *endocarditis* – is the inflammation of the endocardium; *pancarditis* – is the inflammation of the entire heart: the pericardium, the myocardium and the endocardium
2.	Raynaud's phenomenon	Is a medical condition in which the spasm of small arteries causes episodes of reduced blood flow to end arterioles. Typically, the fingers, and less commonly, the toes, the nose, ears, or lips are involved. The episodes classically result in the affected part turning white and then blue. Often, numbness or pain occurs. As blood flow returns, the area turns red and burns. The episodes typically last minutes but can last several hours.
3.	Malar rash (also called butterfly rash)	Is a medical sign consisting of a characteristic form of facial rash. It is often seen in SLE. A malar rash is red or purplish and mildly scaly. It has the shape of a butterfly, and involves the bridge of the nose. Notably, the rash spares the nasolabial folds of the face, which contributes to its characteristic appearance. It is usually macular with sharp edges, and not itchy.
4.	Discoid lupus erythematosus	Is the most common type of chronic cutaneous lupus, an autoimmune skin condition on the SLE spectrum of illnesses. It presents with red painful, inflamed, coin-shaped patches of skin with a scaling and crusty appearance, most often on the scalp, cheeks, and ears. The lesions can then develop severe scarring, and the centre areas may appear lighter in color with a rim darker than the normal skin.
5.	Lupus anticoagulant	Is an immunoglobulin that binds to phospholipids and proteins associated with the cell membrane. Lupus anticoagulant in living systems cause an increase in inappropriate blood clotting. In vivo, the antibodies are thought to interact with platelet membrane phospholipids, increasing adhesion and aggregation of platelets, which accounts for the in vivo prothrombotic characteristics.

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

Entry criterion
Antinuclear antibodies (ANA) at a titer of ≥1:80 on HEp-2 cells or an equivalent positive test (ever)

↓

If absent, do not classify as SLE
If present, apply additive criteria

↓

Additive criteria
Do not count a criterion if there is a more likely explanation than SLE.
Occurrence of a criterion on at least one occasion is sufficient.
SLE classification requires at least one clinical criterion and ≥10 points.
Criteria need not occur simultaneously.
Within each domain, only the highest weighted criterion is counted toward the total score§.

Clinical domains and criteria	Weight	Immunology domains and criteria	Weight
Constitutional		***Antiphospholipid antibodies***	
Fever	2	Anti-cardiolipin antibodies OR	
Hematologic		Anti-β2GP1 antibodies OR	
Leukopenia	3	Lupus anticoagulant	2
Thrombocytopenia	4	***Complement proteins***	
Autoimmune hemolysis	4	Low C3 OR low C4	3
Neuropsychiatric		Low C3 AND low C4	4
Delirium	2	***SLE-specific antibodies***	
Psychosis	3	Anti-dsDNA antibody* OR	
Seizure	5	Anti-Smith antibody	6
Mucocutaneous			
Non-scarring alopecia	2		
Oral ulcers	2		
Subacute cutaneous OR discoid lupus	4		
Acute cutaneous lupus	6		
Serosal			
Pleural or pericardial effusion	5		
Acute pericarditis	6		
Musculoskeletal			
Joint involvement	6		
Renal			
Proteinuria >0.5g/24h	4		
Renal biopsy Class II or V lupus nephritis	8		
Renal biopsy Class III or IV lupus nephritis	10		

Total score:

↓

Classify as Systemic Lupus Erythematosus with a score of 10 or more if entry criterion fulfilled.

Figure. Classification criteria for systemic lupus erythematosus

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

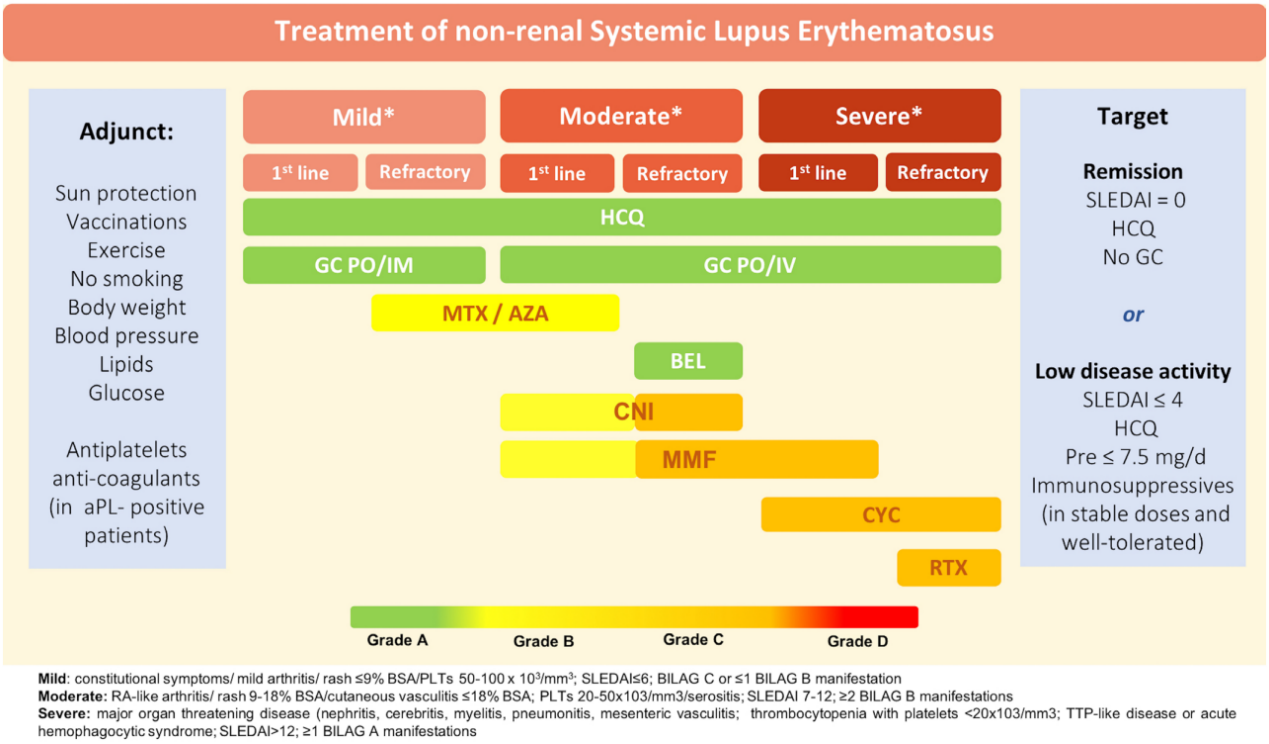


Figure. Treatment of non-renal SLE—recommended drugs with respective grading of recommendation. aPL, antiphospholipid antibodies; AZA, azathioprine; BEL, belimumab; BILAG: British Isles Lupus Assessment Group disease activity index; CNIs, calcineurin inhibitors; CYC, cyclophosphamide; GC, glucocorticoids; 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 nephritis (induction and maintenance therapy); refractory thrombocytopenia; cutaneous manifestations; uncontrolled disease	Diarrhea, nausea; 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 clini-cal 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 cyclophosphamide. 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.

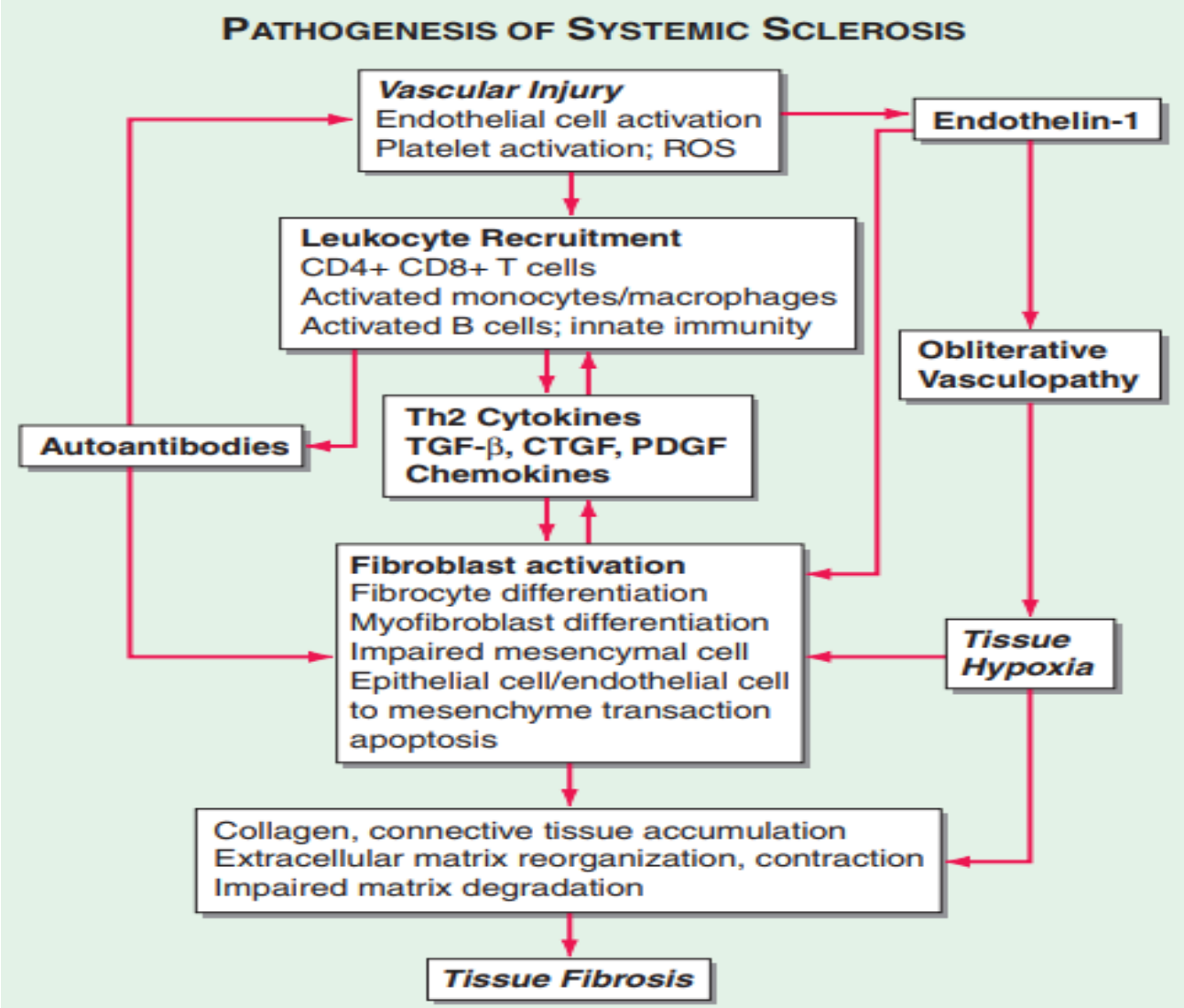
SSc is about 4 times more common among women than men. It is most common among people aged 20 to 50 and is rare in children. SSc can develop as part of mixed connective tissue disease.

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*

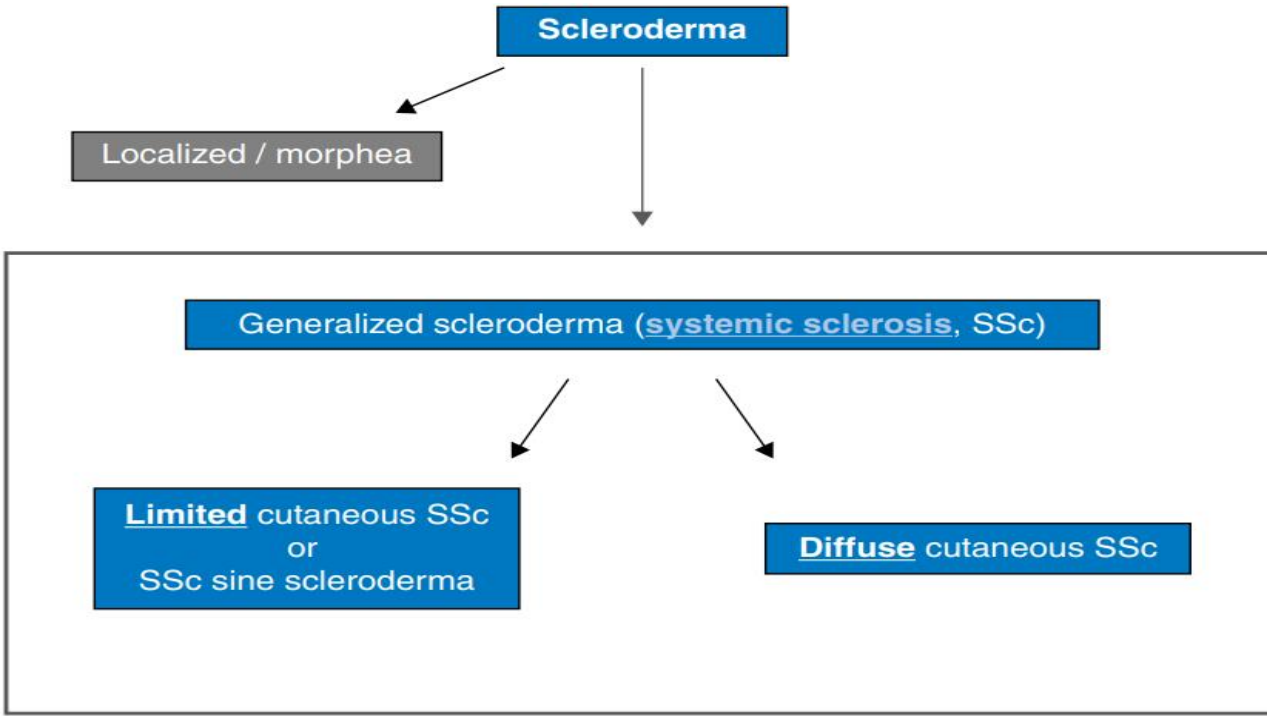
In SSc, the skin develops more compact collagen fibers in the reticular dermis, epidermal thinning, loss of rete pegs, and atrophy of dermal appendages. T cells may accumulate, and extensive fibrosis in the dermal and subcutaneous layers develops. In the nail folds, capillary loops dilate and some microvascular 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,

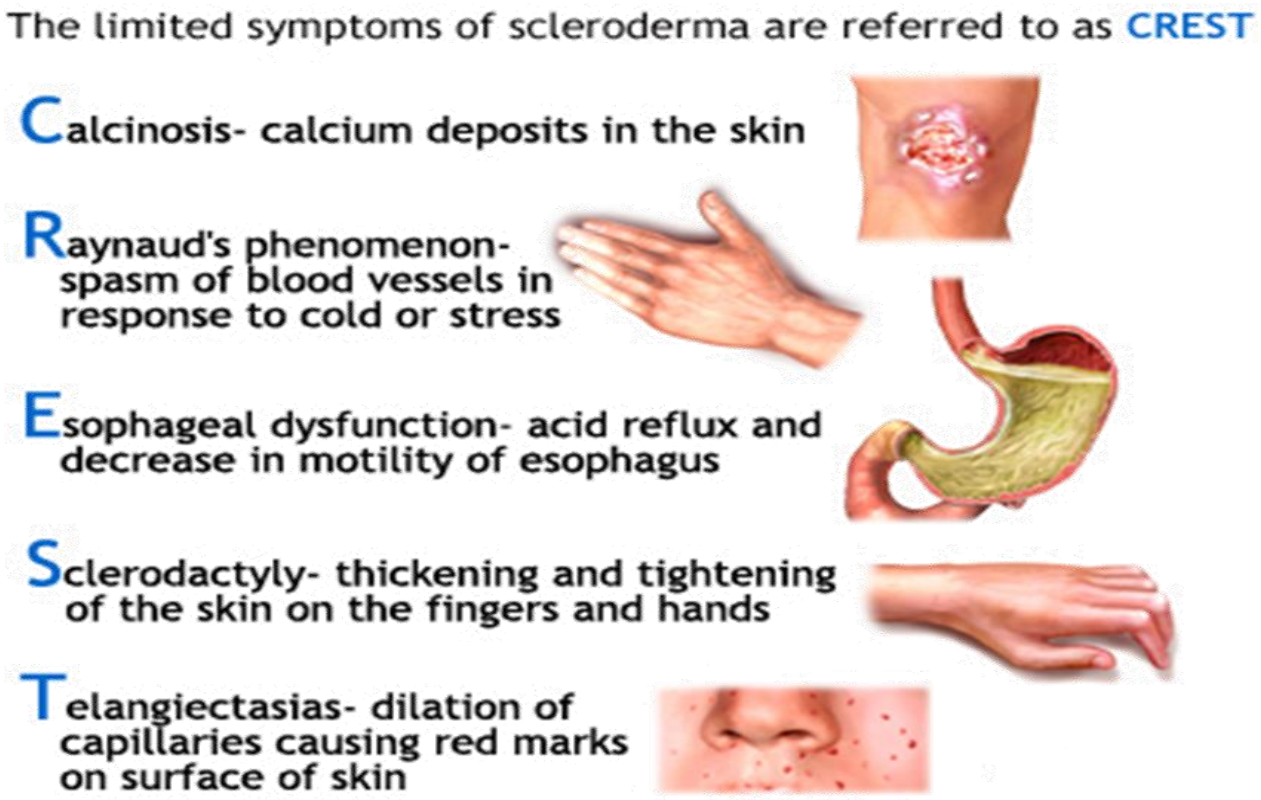
telangiectasias). In addition, SSc can overlap with other autoimmune rheumatic disorders—eg, sclerodermatomyositis (tight skin and muscle weakness indistinguishable from polymyositis) and mixed connective tissue disease.

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.

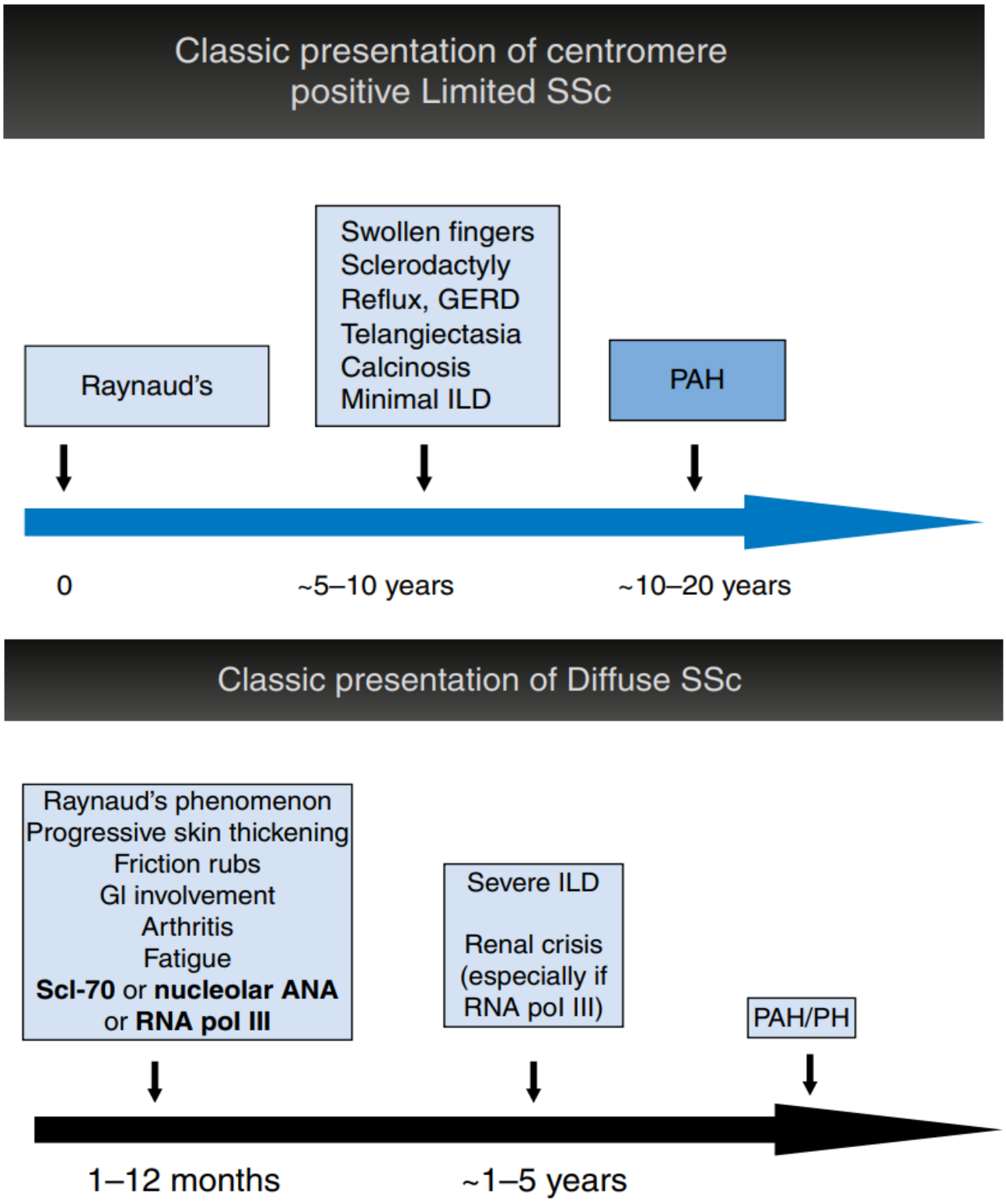
Diagnosis

- 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**, and**vardenafil** are other alternatives for severe Raynaud phenomenon. Patients should dress warmly, wear mittens, and keep their head warm. IV infusions of prostaglandin E1 (**alprostadil**) or**epoprostenol** 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.

Key Points

- Key pathologic changes include skin and joint changes, Raynaud phenomenon, and esophageal changes, but life-threatening effects may involve organs such as the lungs, heart, or kidneys.
- Consider the diagnosis if patients have Raynaud phenomenon, typical musculoskeletal or skin manifestations, or unexplained dysphagia, malabsorption, pulmonary fibrosis, pulmonary hypertension, cardiomyopathies, or conduction disturbances.
- Test for ANA, Scl-70 (topoisomerase I), and anticentromere antibodies.
- Because there is no clear disease-modifying therapy, direct treatment at the involved organs.

Polymyositis and Dermatomyositis

Polymyositis and dermatomyositis are uncommon systemic rheumatic disorders characterized by inflammatory and degenerative changes in the muscles (polymyositis) or in the skin and muscles (dermatomyositis). The most specific skin signs are Gottron papules over the knuckles and a periorbital heliotropic rash. Manifestations include symmetric weakness, some tenderness, and later atrophy, principally of the proximal limb girdle muscles. Complications can include visceral involvement and cancer. Diagnosis is by clinical findings and abnormalities on muscle tests, which may include muscle enzymes, MRI, electromyography, and muscle biopsy. Treatment is with corticosteroids, usually combined with immunosuppressants or IV immune globulin.

The female:male ratio is 2:1. These disorders may appear at any age but occur most commonly from age 40 to 60 or, in children, from age 5 to 15.

Etiology

The cause seems to be an autoimmune reaction to muscle tissue in genetically susceptible people. Familial clustering occurs, and HLA subtypes -DR3, -DR52, and -DR6 seem to be the genetic predisposition. Possible inciting events include viral myositis and underlying cancer. Picornavirus-like structures have been found in muscle cells, but their significance is not known, and viruses can trigger similar disorders in animals. The association of cancer with dermatomyositis (less so with polymyositis) suggests that a tumor may incite myositis as the result of an autoimmune reaction against a common antigen in muscle and tumor.

Pathophysiology

Pathologic changes in both disorders include cellular damage and atrophy, with variable degrees of inflammation. Muscles in the hands, feet, and face are affected less than other skeletal muscles. Involvement of muscles in the pharynx and upper esophagus and occasionally the heart

can impair the functions of those organs. Inflammation may occur in joints and lungs, especially in patients with antisynthetase antibodies.

Dermatomyositis is characterized by immune complex deposition in the vessels and is considered a complement-mediated vasculopathy. In contrast, the main pathophysiologic abnormality in polymyositis is direct T cell-mediated muscle injury.

Classification

Myositis has been divided into several subtypes:

- Primary idiopathic polymyositis can occur at any age and does not involve the skin.
- Primary idiopathic dermatomyositis is similar to primary idiopathic polymyositis but also involves the skin.
- Polymyositis or dermatomyositis associated with cancer can occur at any age but is most common among older adults; the cancer can develop up to 2 yr before or after the myositis.
- Childhood dermatomyositis can be associated with systemic vasculitis.
- Polymyositis or dermatomyositis can occur with an associated disorder such as progressive systemic sclerosis, mixed connective tissue disease, RA, SLE, or sarcoidosis.

Inclusion body myositis is a separate disorder that has clinical manifestations similar to chronic idiopathic polymyositis; however, it develops at an older age, frequently involves distal muscles (eg, hand and foot muscles), has a longer duration, responds poorly to therapy, and has a different histologic appearance.

Symptoms and Signs

Onset of polymyositis may be acute (particularly in children) or insidious (particularly in adults). Polyarthralgias, Raynaud phenomenon, dysphagia, pulmonary symptoms, and constitutional complaints (notably fever, fatigue, and weight loss) may also occur.

Muscle weakness may progress over weeks to months. However, it takes destruction of 50% of muscle fibers to cause symptomatic weakness (ie, muscle weakness indicates advanced myositis). Patients may have difficulty raising their arms above their shoulders, climbing steps, or rising from a sitting position. Patients may become wheelchair-bound or bedridden because of weakness of pelvic and shoulder girdle muscles. The flexors of the neck may be severely affected, causing an inability to raise the head from the pillow. Involvement of pharyngeal and upper esophageal muscles may impair swallowing and predispose to aspiration. Muscles of the hands, feet, and face escape involvement. Limb contractures may eventually develop.

Joint manifestations include polyarthralgia or polyarthritis, often with swelling, effusions, and other characteristics of nondeforming arthritis, which occur in about 30% of patients. However, joint manifestations tend to be mild. They occur more often in a subset with Jo-1 or other antisynthetase antibodies.

Visceral involvement (except that of the pharynx and upper esophagus) is less common in polymyositis than in some other rheumatic disorders (eg, SLE, systemic sclerosis). Occasionally, and especially in patients with antisynthetase antibodies, interstitial pneumonitis (manifested by dyspnea and cough) is the most prominent manifestation. Cardiac arrhythmias, especially including conduction disturbances or ventricular dysfunction, can occur. GI symptoms, more common among children, are due to an associated vasculitis and may include hematemesis, melena, and ischemic bowel perforation.

Skin changes, which occur in dermatomyositis, tend to be dusky and erythematous. Periorbital edema with a purplish appearance (heliotrope rash) is relatively specific for dermatomyositis. Elsewhere, the rash may be slightly elevated and smooth or scaly; it may appear on the forehead, V of the neck and shoulders, chest and back, forearms and lower legs, elbows and knees, medial malleoli, and radiodorsal aspects of the proximal interphalangeal and metacarpophalangeal joints (Gottron papules—also a relatively specific finding). The base and sides of the fingernails may be hyperemic or thickened. Desquamating dermatitis with splitting of the

skin may evolve over the radial aspects of the fingers. The primary skin lesions frequently fade completely but may be followed by secondary changes (eg, brownish pigmentation, atrophy, scarring, vitiligo). Rash on the scalp may appear psoriaform and be intensely pruritic. Subcutaneous calcification may occur, particularly in children.

Diagnosis

- Clinical criteria
- Muscle biopsy (definitive)

Polymyositis should be suspected in patients with proximal muscle weakness with or without muscle tenderness. Dermatomyositis should be suspected in patients with a heliotropic rash or Gottron papules, even without myositis, and in patients with symptoms of polymyositis and any skin findings compatible with dermatomyositis. Polymyositis and dermatomyositis share certain clinical findings with systemic sclerosis or, less frequently, with SLE or vasculitis. Establishing the diagnosis requires as many as possible of the following 5 criteria:

- Proximal muscle weakness
- Characteristic rash
- Elevated serum muscle enzymes (if CK is not elevated, aminotransferases or aldolase [which are less specific than CK])
- Characteristic electromyographic or MRI muscle abnormalities
- Muscle biopsy changes (the definitive test)

Muscle biopsy excludes some similar conditions such as inclusion body myositis and postviral rhabdomyolysis. Biopsy findings can be variable, but chronic inflammation and muscle degeneration and regeneration are typical. A definite diagnosis made by muscle biopsy is recommended before treatment of polymyositis to exclude other muscle disorders. To increase the sensitivity of the biopsy results, the biopsy sample should be obtained from a muscle that has one or more of the following characteristics:

- Weakness on clinical examination
- Inflammation identified on MRI
- Contralateral pair of a muscle shown to be abnormal on electromyography

Laboratory studies can increase or decrease suspicion for the disorder, assess its severity, identify overlaps, and help detect complications. Autoantibodies should be tested. Antinuclear antibodies (ANA) are positive in up to 80% of patients. Detailed testing of ANA, when present, is important in identifying other overlap syndromes, most often those with another autoimmune disorder. About 30% of patients have myositis-specific autoantibodies: antibodies to aminoacyl-tRNA synthetases (anti-synthetase antibodies), including anti–Jo-1; antibodies to signal recognition particle (SRP—anti-SRP antibodies); and antibodies to Mi-2, a nuclear helicase. The relationship between these autoantibodies and disease pathogenesis remains unclear, although antibody to Jo-1 is a significant marker for fibrosing alveolitis, pulmonary fibrosis, arthritis, and Raynaud phenomenon.

Periodic measurement of CK is helpful in monitoring treatment. However, in patients with widespread muscle atrophy, levels are occasionally normal despite chronic, active myositis. Muscle biopsy, MRI, or high CK levels can often differentiate a relapse of polymyositis from corticosteroid-induced myopathy. Aldolase is a less specific marker for muscle injury than CK.

Cancer screening is recommended by some authorities for patients ≥ 40 yr who have dermatomyositis or for patients ≥ 60 yr who have polymyositis because these patients often have unsuspected cancers. Screening should include a physical examination that includes breast, pelvis, and rectum (with occult blood testing); CBC; biochemical profile; mammogram; carcinoembryonic antigen; urinalysis; chest x-ray; and any other tests appropriate based on patient's age. Additional investigation should be based on history and physical examination findings. Some authorities

recommend CT of the chest, abdomen, and pelvis. Younger patients without symptoms of cancer need not undergo screening.

Prognosis

Long remissions (even apparent recovery) occur in up to 50% of treated patients within 5 yr, more often in children. Relapse, however, may still occur at any time. Overall 5-yr survival rate is 75% and is higher in children. Death in adults is preceded by severe and progressive muscle weakness, dysphagia, undernutrition, aspiration pneumonia, or respiratory failure with superimposed pulmonary infection. Polymyositis tends to be more severe and resistant to treatment in patients with cardiac or pulmonary involvement. Death in children may be a result of bowel vasculitis. Cancer, if present, generally determines the overall prognosis.

Treatment

- Corticosteroids

- Sometimes immunosuppressants (eg, **methotrexate**, **azathioprine**, **mycophenolate mofetil**, **rituximab**, **cyclosporine**, IV immune globulin)

Physical activities should be modestly curtailed until the inflammation subsides. Corticosteroids are the drugs of choice initially. For acute disease, adults receive **prednisone** ≥ 40 to 60 mg po once/day. Serial measurements of CK provide the best early guide of therapeutic effectiveness, falling toward or reaching normal in most patients in 6 to 12 wk, followed by improved muscle strength. Once enzyme levels have returned to normal, **prednisone** can be gradually reduced. If muscle enzyme levels rise, the dose is increased. Patients who seem to recover can have treatment gradually withdrawn with close monitoring, but most adults require chronic maintenance with **prednisone** (up to 10 to 15 mg/day). Children require initial doses of **prednisone** of 30 to 60 mg/m^2 once/day. In children, it may be possible to stop **prednisone** after ≥ 1 yr of remission.

Occasionally, patients treated chronically with high-dose corticosteroids become increasingly weak because of a superimposed corticosteroid myopathy.

If a patient does not to respond to corticosteroids, depends on a high to moderate dose of corticosteroids, or develops a corticosteroid myopathy or another complication that necessitates stopping or decreasing **prednisone**, immunosuppressants (eg, **methotrexate**, **azathioprine**, **mycophenolate mofetil**, **rituximab**, **cyclosporine**, IV immune globulin) should be tried. Some clinicians combine **prednisone** with an immunosuppressant at the time treatment is initiated. Some patients have received only **methotrexate** (generally in higher doses than used for RA) for ≥ 5 yr. IV immune globulin can be effective in some patients refractory to drug treatment, but the prohibitive cost has discouraged comparative trials.

Myositis associated with cancer or inclusion body myositis usually is more refractory to corticosteroids. Cancer-associated myositis may remit if the tumor is removed.

People with an autoimmune disorder are at higher risk of atherosclerosis and should be closely monitored. Patients on long-term corticosteroid therapy should receive osteoporosis prophylaxis. Prophylaxis for opportunistic infections, such as Pneumocystis jirovecii, should be added if combination immunosuppressive therapy is used.

Key Points

- Muscle weakness indicates advanced myositis.

- Heliotropic rash and Gottron papules are relatively specific for dermatomyositis.

- To establish the diagnosis, look for characteristic muscle weakness and rash, elevated CK level, and muscle changes on electromyography or MRI.

- If necessary, do a muscle biopsy to confirm the diagnosis.

- Screen patients ≥ 40 yr with dermatomyositis and patients ≥ 60 yr with polymyositis for cancer.

- Treat most patients with corticosteroids and sometimes other immunosuppressants.

Equipment: training room, cardiac patient examination simulator Harvey, 6-channel electrocardiograph CARDIOLINE, Echocardiography machine.

Lesson duration: 4 hours

Plan

1. Organizational moment (greetings, checking the audience, the message of the topic, the purpose of the lesson, the motivation of applicants to study the topic).
2. Control of basic knowledge (initial survey with tests of the STEP 2 format – attached, check of workbooks on the topic):
2.1. Requirements for theoretical readiness of applicants to perform practical classes.
Knowledge requirements:

- Definition of Systemic connective tissue disease
- Current views on the etiology and pathogenesis of Systemic connective tissue disease
- Classification of Systemic connective tissue disease
- Clinical presentation of Systemic connective tissue disease
- Diagnostic of Systemic connective tissue disease, Jones criteria
- Differential diagnostic
- Complications of Systemic connective tissue disease
- Treatment of Systemic connective tissue disease
- Prognosis for patients with Systemic connective tissue disease
- Primary and secondary prophylaxis Systemic connective tissue disease

List of didactic units:

- to collect in detail the anamnesis of the disease;
- to conduct a physical examination of the patient, to identify and assess changes in his condition;
- make a plan for additional examination, evaluate its results;
- formulate and substantiate a preliminary and clinical diagnosis of Systemic lupus erythematosus, taking into account the severity of disorders according to the classification, comprehensive assessment of patients;
- assessment of possible complications of Systemic lupus erythematosus;
- evaluation of the results of general clinical examination, laboratory analysis of blood, data of electrocardiogram, echocardiogram, X-rays, CTs, MRIs, ultrasound, etc.

The tests for self-control with standard answers.

1. In the development of the inflammation processes glucocorticoids reduce the level of certain most important active enzyme. It results also in the reducing of the synthesis of prostaglandins and leucotrienes which have a key role in the development of inflammation processes. What is the exact name of this enzyme?

A Phospholipase A2
B Arachidonic acid
C Lipoxygenase
D Cyclooxygenase – 1
E Cyclooxygenase – 2

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

6. In the development of the inflammation processes glucocorticoids reduce the level of certain most important active enzyme. It results also in the reducing of the synthesis of prostaglandins and leucotrienes which have a key role in the development of inflammation processes. What is the exact name of this enzyme?

A. Phospholipase A2
B. Arachidonic acid
C. Lipoxygenase
D. Cyclooxygenase – 1
E. Cyclooxygenase – 2

7. A patient has complained of great weakness for 6 years. He fell seriously ill, the illness is accompanied by body temperature rise, indisposition, pain in joints and along the legs muscles. Objectively: violet-bluish erythema around eyes and over knee joints. HR- 120/min, heart sounds are weak. Blood count: leukocytes - $12*10^9$/L, ESR- 40 mm/h. What is the most probable diagnosis?

A. Rheumathoid arthritis
B. Systemic lupus erythematosus
C. Dermatomyositis
D. Atopic dermatitis
E. Reactive polyarthritis

8. 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

9. A 58-year-old patient complains about sensation of numbness, sudden paleness of II-IV fingers, muscle rigidness, intermittent pulse. The patient presents also with polyarthralgia, dysphagia, constipations. The patient's face is masklike, solid edema of hands is present. The heart is enlarged; auscultation revealed dry rales in lungs. In blood: ESR- 20 mm/h, crude protein - 85/l, gamma-globulines - 25\%. What is the most likely diagnosis?

A. Systemic lupus erythematosus
B. Dermatomyositis
C. Rheumatoid arthritis
D. Systemic scleroderma
E. Raynaud's disease

10. A 32 year old patient complains about pain in small joints of her hands, paresthesia at the tips of fingers, weakness, difficult diglutition. She has been suffering from this for 13 years. Objectively: face amimia, shortening of nail bones, skin indurations in the area of shoulder girdle are present. Roentgenological examination of lungs revealed basal pneumosclerosis. Fibrogastroscopy revealed esophagus constriction in its cardial part. Blood count: leukocytes - $9,8*10^9$/l, ESR - 22 mm/h, γ-globulin - 22%. What is the most probable diagnosis?

A. Systemic lupus erythematosus
B. Systemic scleroderma
C. Rheumatoid arthritis
D. Dermatomyositis
E. Myxedema

11. A 38 year old man complains about mild pain and muscle weakness of shoulder and pelvic girdles and back that has been progressing for the last 3 weeks. He has also significant problems with getting up, going up and down the stairs and shaving. It is suspected that the patient is suffering from dermatomyositis. Blood count: Hb - 114 g/l, leukocytes - $10,8*10^9$/l, eosin - 9%, ESR - 22 mm/h, C-reactive protein (++). Change of the following laboratory factor will be of the greatest diagnostic importance:

A. Sialic acids
B. Ceruloplasmin
C. Creatine phosphokinase
D. Antibodies to the native DNA
E. Gamma-globulins

12. A 36-year-old female patient complains of general weakness, edemata of her face and hands, rapid fatiguability during walking, difficult diglutition, cardiac irregularities. These symptoms turned up 11 days after a holiday at the seaside. Objectively: face erythema, edema of shin muscles. Heart sounds are muffled, AP is 100/70 mm Hg. In blood: AST activity is 0,95 millimole/h*l, ALT - 1,3 millimole/h*l, aldolase - 9,2 IU/l, creatine phosphokinase - 2,5 millimole P/g*l. What method of study would be the most specific?

A. Muscle biopsy
B. ECG
C. Echocardiogram
D. Electromyography
E. Determination of cortisol concentration in blood and urine

Standard answers: 1-A, 2-B, 3-A, 4-D, 5-E, 6-A, 7-C, 8-A, 9-D, 10-B, 11-C, 12-A.

Clinical case with standard answers

Patient M., age 21, fell ill after hypothermia. The disease began with the rise of temperature to 39, refractory to antibiotics, weakness, weight loss, pain and swelling in the knee, ankle and elbow joints, increasing of submandibular lymph nodes.

On examination: a serious condition. On the face erythema "butterfly". The oral mucosa - ulcers. Submandibular lymph nodes were enlarged. Swelling of the knee, ankle, elbow joints. The skin over the joints, flushed and hot to the touch. Movement of the joints painful. Pulse 118 in 1 min, rhythmic. Blood pressure 90/40 mmHg Borders of the heart: the right shifted by 1 cm to the right of the right edge of the sternum, upper-upper edge of the 2 rib, the left- +2 cm to the left . Cardiac sounds weakened. At the lower parts of the lungs harsh breathing. The liver + 2 cm, soft and sensitive.

Analysis of blood: E 2,8 $x10^{12}$ / l, WBC $3.2x10^{9}$ / l, platelets $90x10^{9}$ / l, total protein 56 g / l, albumin 35%, α -2-globulins-12%, γ-globulin 28%, fibrinogen 5,5 g / l.

Urine: daily protein - 5 g / day ; weight 1020, leukocytes 6-8 in the field of view, 20-25 red blood cells in the field of view, hyaline cylinders 3-5 in the field of view.

Questions:

1. Diagnosis?
2. Present diagnostic criteria of the disease?
3. Diagnosis?
4. Treatment?

Answering standards

1. SLE, III degree of activity with the defeat of the skin (erythema - "Butterfly"), mucous membranes (oral mucosa ulcers), joints (polyarthritis), serous membranes (pericarditis), kidneys (nephritis with nephrotic syndrome), with hematological disorders.

2. Diagnostic criteria of SLE patient: erythema - "Butterfly", the oral mucosa ulcers, arthritis of 2 or more joints, serositis, renal, haematological disorders.

3. X-ray of the chest, echo-cardiography, Rehberg test. Immunological markers of disease: ANF, antibodies to DNA.

4. Corticosteroids (prednisone (t.5mg, № 100) at a dose of 1 mg / kg body weight), • cytostatics (cyclophosphamide -vial with dry substance for injection of 200mg, 500mg and 1000mg, № 10 to 200mg i / m 2 per week). • In case of failure-pulse therapy.

Collection of complaints and anamnesis in patients with internal diseases

1. Friendly facial expression, smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Collection of complaints and medical history of the patient.
5. Explanation of survey results.
6. Explanation of actions (hospitalization, conducting certain examinations) that are planned to be performed in the future.
7. End the conversation.

Physical methods of examination of patients with internal diseases

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Explain to the patient which examination will be performed and obtain his consent.
6. Warning about the possibility of unpleasant feelings during the examination.
7. Preparation for the examination (clean warm hands, trimmed nails, warm stethoscope, if necessary – use a screen).
8. Conducting an examination (demonstration of clinical skills).
9. Explanation of survey results.

10. End the conversation.

Reporting the results of the examination to patients with internal diseases.

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the results of a particular examination.
5. Involve the patient in the interview (compare the results of this examination with previous results, find out if they understand your explanations).
6. End the conversation.

Planning and forecasting the results of conservative treatment:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the need for prescribed treatment.
5. Involvement of the patient (emphasis on the peculiarities of the drugs, duration of administration, possible side effects; find out whether the patient understands your explanations).
6. End the conversation.

Treatment prognosis message:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the expected results of the prescribed treatment.
5. Involve the patient in the conversation (emphasis on the importance of continuous treatment, adherence to the prescribed treatment regimen, finding out whether your explanations are clear to the patient).
6. End the conversation.

Work 1.

1. Collection of complaints, anamnesis, examination of a patient with Systemic lupus erythematosus.
2. Detection of clinical symptoms.
3. Grouping of symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data (clinical analysis of blood, urine, biochemical analysis of blood, chest X-ray or chest CT-scan, X-ray of joints or MRI or ultrasound of joints, ECG, echocardiography, etc.).
6. Carrying out of the differential diagnosis with other arthritis.
7. Formulation of the clinical diagnosis.
8. Determining the degree of disability.

Work 2.

Appointment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the cathedral library with thematic literature.

The student fills in the protocol of examination of the patient in writing. An example of the initial examination of the patient is attached.

Control materials for the final stage of the lesson:

Tasks for self-control with answers.

CLINICAL CASE # 1

Patient N., female, 43 years old. 5 years ago the pain first appeared in the small joints of hands, elbows, noted moderate swelling of these joints, but didn't visit the doctor, took analgesics. In the same period observed the appearing of persistent erythema on the cheeks and spine of the nose in the spring and summer, from time to time without apparent cause increased body temperature to subfebrile level. After 4 years of onset, the patient began to feel the pain in almost all joints in the lumbar region. Was treated on an outpatient department due to lumbosacral degenerative disc disease, took NSAIDs, physiotherapy with little effect. Over the past 6 months has note shortness of breath at mild exertion, edema of legs in the evening, the pain in the right hypochondrium and the right half of the chest, lost weight on 10 kg. 2 weeks before visiting the doctor noticed an increase in the size of the abdomen, the appearance of pain behind the breastbone of a continuing nature, which facilitated by sitting in knee-elbow position, shortness of breath, temperature was increased daily until 38-38,5 C.

At admission to the hospital: the state of medium gravity, low nutrition, pale skin, erythema on the cheeks and spine of the nose. Palpable moderate increased posterior-cervical, axillary lymph nodes, they were movable, elastic, painless.On examination of the joints has been a slight defiguration of proxymal interphalangeal, metacarpophalangeal joints, deformities of the joints were observed, palpation is moderately painful Percussion of the chest: revealed a shortening of percussion sound in the lower parts of the lungs from the level of 4 intercostal space, in this area of dulness the breath is not conducted above the dulling auscultated finely resonant rales. RR - 26 per minute. The left border of the relative cardiac dullness in 5 intercostal space on the mid-clavicular line, sounds are muffled, rhythmic, pericardium rub, heart rate - 100 per min., Blood pressure - 110/60 mmHg. Abdomen increased in size, flattened, with the percussion is determined by the blunting of the lateral flanks of the abdomen, moves down at the change of body position. The liver + 3 cm. Peripheral edema. Positive Pasternatsky's symptom from both sides.

CBC: ESR 45 mm / h, Hb - 87 g / l, E - 3,8 $x10^{12}$ / l, color index - 0,68, L. - 2,6 $x10^{9}$ / l, b - 0% e - 2%, b - 8%, s - 71%, lymph. - 13%, Mon. - 6%, Pl - $40x10^{9}$ / l.

Urine analysis: a transparent, weakly acidic, protein - 0,99 g / l, no sugar, L. - 2-6 in f / v., Er. - 4-8-12 in f / v., hyaline cylinders - 2-4 in f / v.

Glucose: 4,23 mmol / l, PTI - 95%. CRP - 98 mg / l, Serum iron - 20 mmol / l, rheumatoid factor - 0. Immunological tests: CIC - 120 units., antibody to native DNA - 360 Me, ANF - 1 / 28. LE cells + + +.

Questions:

1. Primary clinical diagnosis?
2. Plan of additional investigation?
3. Differential diagnosis?
4. Treatment?

Answering standards:

1. Systemic lupus erythematosus, subacute, activity grade 2, lymphadenopathy, arthritis, polyserositis - pleurisy, pericarditis, pneumonitis, nephritis. Complication: HF II-B.

2. CBC, general urinalysis, electrocardiogram, to confirm the nosologic units - immunological blood test for antibodies to native DNA, antinuclear factor, a blood test for LE cells,

to confirm the nature of the lung (pleurisy, pneumonia) - Chest X-ray, Pleural cavity with ultrasound detection of the number fluid, pleural puncture with analysis of exudate general and LE-cells, in order to clarify the nature of the defeat of the heart (pericarditis, lupus-carditis?) - Ehocardioscopy, to assess kidney function – GFR, Zimnitskiy test.

3. Rheumatoid arthritis with systemic manifestations, lymphogranulomatosis (polilymphoadenopaty, pleurisy), tuberculosis (pneumonia, pleurisy).

4. The treatment: reduction of inflammatory process, the selection of continuous immunosuppressive therapy.

CLINICAL CASE # 2

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

1. SLE, acute, active phase.
2. 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.
3. It should be a differential diagnosis of rheumatoid arthritis, rheumatic heart disease, nodular periarteriitis etc. connective tissue diseases.
4. Glucocorticoids, aminochinoline derivatives, cytostatics.
5. Due to severity of activity - physical therapy procedures are contraindicated.

CLINICAL CASE # 3

Patient S., aged 28, was admitted to regional hospital with complaints of pain in small joints of hands, low-grade fever, weight loss, hair loss. She felt ill for 10 months. After pregnancy, there were pains in all joints of the hands and feet without swelling, weakness, recurrent episodes of rising temperatures, worsened appetite, was losing weight. When appeared hyperemia of face, swelling of the legs and face, shortness of breath, pain in the lower regions of the thorax visited the doctor.

Objectively: the temperature of 37,7, swelling hands, defiguration of proximal interphalangeal joints, hyperemia of the cheeks, enlargement of the heart to the left, the deaf sounds, tachycardia, systolic murmur on apex. Blood pressure 150/100 mmHg.Vesicular breathing.

Blood tests: Er. - 3.2 * 10^{12} / l, Hb - 106 g / l, L. - 3,4 * 10^{9} / l, ESR - 60 mm / hour. Urine:1016, protein 1.65 g / l, L. - 8-10 in f / v, hyaline cylinders 4-5 f / v.

X-rays of the chest: thickening of the interlobar pleura, high standing of the diaphragm on the right.

Questions:

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

Answering standards

1. Systemic lupus erythematosus.
2. LE-cells, antibodies to DNA, RF, CRP, renal function tests (Rehberg, Zimnitskiy).
3. During the initial manifestations must be differentiated with RA, rheumatism.
4. A) methylprednisolone (pulse therapy) 1000 mg / d / v, Cap., № 3, in a subsequent prednisolone 60-90 mg / day to obtain remission. B) cyclophosphamide 1.0 g / in №, later on 200 mg every other day. Plasmapheresis № 3. Repeated courses every 3 months. (Pulse-therapy - metipred and cyclophosphamide).
5. Contraindicated.

CLINICAL CASE # 4

Patient P., female, aged 26, was admitted to the cardiology department complaining of pain in the joints, muscles, raising the temperature to 39^{0}, headache, edema, shortness of breath. This condition occurred after insolation.

Objective: the state of medium gravity, hyperemic cheeks, his face puffy, there is edema of the lower extremities, ascites. Blood pressure 160/100 mmHg Pulse 94 per minute. Cardiac sounds weakened. In the lower parts of lungs during percussion shortening of lung sound.

Urinalysis: the relative density1018, protein 16.2 g / l, red blood cells cover the entire field of view, leucocytes 10 in f/v, cylinders: hyaline and granular 2-3 in f/v

Total protein 56 g / l, cholesterol 8 mmol / l, urea 12 mmol / l, creatinine 0.16 mmol / L, glomerular filtration, 42 ml / min.

Radiologically: the fluid in the pleural cavity, lung fields clear.

Questions:

1. Highlight the main symptoms?
2. What diseases have you suspect?
3. Formulate a primary diagnosis, justify it?
4. What investigation you need for verify the diagnosis?

Answering standards

1. Edematous nephrotic, urinary, feverish, articular.
2. Acute glomerulonephritis, systemic lupus erythematosus (SLE).
3. Systemic lupus erythematosus, acute course. Lupus glomerulonephritis with nephrotic syndrome and initial signs of kidney failure.
4. Blood examination for lupus cells, antinuclear antibody titer, biopsy of the kidneys.

CLINICAL CASE # 5

Patient N., female, 43 years old, complaints with the growing general weakness and stiffness, marked limitation of motion in joints of hands and feet, shortness of breath at the slightest exertion and palpitation.

She is ill for 14 years. Disease was preceded by trauma and cooling, and then came the increased chilliness and cyanosis of the fingers, then trophic disorders and dense edema of hands

and feet. Later joined by pain in joints and muscles, seal skin, deformity of joints and spine, growing, general stiffness and immobility. During the illness the patient had lost 30 kg in weight.

Examination: impairment of all the fingers: cold, covered with thick shiny skin, deformity ("bird legs"). A large deformation and shortening of the fingers, they are in palmar flexion. Atrophy of the muscles. Face without mimic, like mask with thinned glossy skin, thinning of the nose, lips, ears and mouth narrow slit.

X-ray of hands: sever deformation with flexion contracture, the narrowing of the joint cavity. Partial osteolysis of terminal phalanges. In the joints of the wrist joint narrowing of gaps. Moderate osteoporosis.

Questions:

1. Primary clinical diagnosis?
2. Plan of investigation for revealing visceral pathology?
3. Differential diagnosis?
4. Treatment?

Answering standards

1. Systemic scleroderma, subacute with lesions of the skin, joint-muscular syndrome with contractures, suspected pneumosclerosis, cardiosclerosis.

2. To detect visceral injuries: lung - X-rays (basal pneumosclerosis), esophagus (narrowing in the lower 1 / 3), heart - ECG, echocardiography, etc. To clarify expression of immune-inflammatory syndrome – CBC, proteinogramme, fibrinogen, CRP, LE cells, RF.

3. Rheumatoid arthritis, SLE during the early manifestations of disease.

4. Antifibrosis - D-penicillamine 300 mg under the control of hemogram (white blood cells, platelets); topically in the form of application 12-14 lidasa or by 64 units. courses.; - vasoactive drugs and disaggregants, Ca channel blockers (nifedepin). Preparations of nicotinic acid, trental; - Anti-inflammatory drugs - prednisolone 20-30 mg per day for a process activity in the lungs of the patient.

CLINICAL CASE # 6

Patient S., aged 48, female, fell ill acutely with increasing temperature to 38,80, progressive weakness, aches in shoulder and pelvic girdle muscle and arthralgia. Then joined purple periorbitale swelling of eyelid skin, erythema on her face, region of seals bluish purple color in the shoulders and hips. Because of the weakness in the muscles could not walk.

In the analysis of blood leukocytosis - 13,6 * 10^9 / L, moderate anemia (Hb 114 g / l), ESR 32 mm / hour.

In the history: mastopathy within 4 years. Is registered in the Oncology Center.

Questions:

1. Primary clinical diagnosis?
2. Plan of additional investigation?
3. Differential diagnosis?
4. Treatment?
5. Does your patient in the dispensary observation? What experts?

Answering standards

1. Dermatomyositis, Paraneoplastic, acute, III degree of activity.

2. Activity of muscle enzymes (CPK, LDH, AST, ALT) - a muscle biopsy - the identification of myofibrillar degeneration and necrosis, perivascular and interstitial infiltration of lymphocytes, histiocytes and plasma cells - pathognomonic for dermatomyositis. - Study of immune activity (antinuclear antibodies, antinuclear factor, antibodies to DNA) - acute phase reaction (proteinogramm, CRP, seromucoid, fibrinogen).

3. Within the group of diffuse connective tissue diseases, in particular with SLE in connection with the combination of skin, joint, muscle, and febrile syndromes in women 48 years.

4. The detection of neoplasm, probably early operative or other active treatment of the tumor, determines prognosis Paraneoplastic dermatomyositis. As in idiopathic and in Paraneoplastic dermatomyositis possible early administration of steroids (prednisone or methylprednisolone) in suppressing dose (not less than 1 mg per 1 kg) 60-80 mg, which remains high (not less than 40 mg) during the first year treatment.

5. Observation oncologist and rheumatologist, with appearances at least 2 times a year to avoid recurrence of the tumor and correction of conservative therapy.

CLINICAL CASE # 7

Patient P., aged 32, female, was admitted to hospital in serious condition with complaints of pain in muscles and almost complete immobility, difficulty swallowing, general weakness.

A year ago, there were pain in the legs, then a feeling of weakness, gait became unsteady. A month later, an erythema on the face and neck. Suspected systemic lupus erythematosus. Treatment by prednisolone 15 mg per day without effect, the patient continued to progressively deteriorate, increasing intensity weakness, and soon the patient could not own up to the bus, self-rising from a chair. There were seals in the painful shoulder muscles, with difficulty turned in bed, there were difficulties in swallowing food, liquid food was poured through the nose, appeared hoarseness of voice.

Examination: temperature 37,50, observed seal shoulder muscles, thighs. On palpation painful muscles, there periorbital cyanotic edema, persistent erythema of the face and neck. Joints without visible changes. With great difficulty, raised her head from the bed, could not raise his hands up and hair. The heart was normal. Blood pressure 100/60 mmHg. Liver and spleen were not enlarged.

Blood tests: Er. - 4,0 * 10^{12} / l, Hb - 120 g / l, L - 9 * 10^{9} / l, ESR - 60 mm / hour. Formula normal. Total protein 80 g / l. Urine: no pathology. ECG: moderate muscle changes. Chest x-ray: signs of left-side exudative pleurisy.

Questions:

1. Primary clinical diagnosis?
2. Plan of additional investigation?
3. Differential diagnosis?
4. Treatment?

Answering standards

1. Dermatomyositis, acute, III activity.
2. Activity of muscle enzymes (CPK, LDH, AST, ALT) - a muscle biopsy - the identification of myofibrillar degeneration and necrosis, perivascular and interstitial infiltration of lymphocytes, histiocytes and plasma cells - pathognomonic for dermatomyositis. - Study of immune activity (antinuclear antibodies, antinuclear factor, antibodies to DNA) - acute phase reaction (proteinogramm, CRP, seromucoid, fibrinogen).
3. With polimyositis associated with SLE; with polimyositis associated with tumors.
4. Prednisolone 1 mg / kg body weight up to complete suppression of activity (1 / 2 years - 1 year) in the subsequent maintenance dose is gradually reduced 20-15-10 mg in case of detection of tumor surgical treatment on a background of decline.

CLINICAL CASE # 8

Patient S., female. admitted to the clinic with complaints of weakness, weight loss, swelling of the skin hands, forearms, dark skin, chilliness in the tips of the fingers, blanching of fingers on a cold, pain in large joints. Sick for 3 years.

In the beginning appeared chill fingers, cyanosis and blanching in the cold. During the past 3 months, worried about weakness, dense swelling of hands, forearms, the temperature 37.5. The examination at the rheumatology center: CBC – E. 3,1 x10^{12} / l, Hb 90 g / l, WBC 8,2 x10^{9} / l, ESR 53 mm / h. Total protein 86 g / l, globulins 40%, ANF + peripheral glow.

On examination: low-power, skin dark, tough. Enlargement of lymph. nodes PS 96 in 1 min., rhythm., Blood pressure 100/60 mmHg. Borders of the heart are normal. Cardiac sounds are muffled, short systolic sound on apex. Vesicular breathing in lings. Abdomen: palpation- soft, the liver at the edge of the costal arch.

Questions:

1. Formulate diagnosis?
2. List diagnostic criteria of the disease. What is CREST-syndrome?
3. Standards of examination of patients with this pathology?
4. Standard treatment for patients with this pathology?

Answering standards

1. Systemic scleroderma, activity II, limited form, chronic.
2. Solid edema, Raynaud syndrome, hyperpigmentation of the skin. CREST syndrome is a symptom, including: calcinosis, Raynaud's, esophagitis, sclerodactyly, telangiectasia.
3. X-ray, Echo
4. D-penicillamine 300 mg under the control of hemogram (white blood cells, platelets); topically in the form of application 12-14 lidasa or by 64 units. courses.; - vasoactive drugs and disaggregants, Ca channel blockers (nifedepin). Preparations of nicotinic acid, trental; - Anti-inflammatory drugs - prednisolone 20-30 mg per day for a process activity in the lungs of the patient.

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Appendix 1

An example of the initial examination of the patient

Passport part: Name, European female of 39 years old.

Complaints: of pain in the right flank of the abdomen, in the lumbar region, general weakness, headache.

Anamnesis morbi: Considers herself ill for a year, when the examination revealed protein in the urine (up to a maximum of 5 g/l), erythrocituria up to 10 per view, hyaline casts, hypercholesterolemia, an increase in ESR up to 70 mm/h. She applied for medical help, was tested for HIV, hepatitis B and C, the results were negative, an additional examination by a rheumatologist was recommended. Analysis for ANA - positive, dsDNA - positive.

X-ray of the lungs – No obvious focal and infiltrative changes were found. The interlobar groove on the right is underlined. The roots are heavy. The diaphragm is of the usual configuration. On the right, there is a pleurodiaphragmatic adhesion.

Ultrasound: Signs of chronic cholecystitis. Chronic bilateral pyelonephritis.

CT virtual colonoscopy: Colon cancer was not revealed. Dolichosigma.

Percutaneous puncture biopsy of the left kidney was performed under ultrasound guidance. 3 tissue biopsies were obtained. The material was sent for light microscopy and immunohistochemistry. Conclusion: pathomorphological, histochemical, immunohistochemical, clinical and laboratory data testify in favor of the secondary nature of the lesion - most likely lupus glomerulonephritis (II (mesangial proliferative) morphological classes) with pronounced tubular and moderately expressed interstitial component.

Hospitalization was recommended.

Anamnesis vitae.

She suffered from Botkin's disease in childhood.

Fluoroscopy of the large intestine – Spastic colitis.

On gastric endoscopy: signs of distal reflux esophagitis, focal erythematous reflux gastropathy.

Abdominal ultrasound - kink of the gallbladder. Uric acid diathesis.

X-ray of the bones of the skull - normal

She underwent removal of the uterus without appendages in connection with fibroids.

In the past, giardiasis was detected, and it was successfully treated.

Material and living conditions are satisfactory. Tuberculosis, sexually transmitted diseases, HIV denies. No allergic reactions have been identified. There were no occupational hazards. Hereditary history: the father suffers from gout with the presence of tophi.

Insurance history: currently does not work, has not been on sick leave for the last 12 months.

Status present obectivus: General condition of the patient of moderate severity, clear consciousness. The position in bed is active. The skin and visible mucous membranes are clean. Subcutaneous fat is evenly developed. Percussion over the entire surface of the lungs is a clear pulmonary sound. Auscultation over the lungs is vesicular breathing. Breath rate: 18/min. The boundaries of relative cardiac dullness are not changed. Heart sounds are rhythmic, muffled. BP 100/60 mm Hg, heart rate 72/min. The abdomen is rounded, soft, tender in the right flank, painless in other areas. Sections of the intestine are spasmodic, sensitive to palpation. The liver is at the edge of the ribs, the edge is smooth. The spleen and kidneys are not palpable. The shins are minimally pasty. Pasternatsky's symptom is negative on both sides.

Preliminary diagnosis:

Systemic lupus erythematosus, subacute course, activity 2, lupus glomerulonephritis, mesangioproliferative, II morphological class.

Spastic colitis. Chronic gastritis. Reflux esophagitis. Chronic non-calculous cholecystitis.

Examination plan:

12. Complete blood count,

13. Blood biochemistry,
14. Acute-phase rheumatic tests,
15. Coagulation test,
16. Liver function tests,
17. Kidney function tests,
18. Lipid profile
19. Urinalysis;
20. ECG,
21. Echocardiography,
22. Chest X-ray.

Treatment plan:

9. Bed rest, common diet.
10. Methylprednisolone 1000 mg / day, i.v. infusion once a day, 3 days
11. Methylprednisolone 32 mg / day, orally, in morning, after meal
12. Hydroxychloroquine 200 mg orally during meal OD
13. Ramipril 2,5 mg orally OD
14. Pantoprazole 40 mg i.v. OD
15. Torasemide 20 mg i.v. OD

Appendix 2.

Tests of the initial level of knowledge of the KROK format

Topic 3. Systemic diseases of connective tissue

1. The initial clinical manifestations of SLE most often are:

A. dermatitis, arthritis, serositis

B. endocarditis, pneumonitis, glomerulonephritis

C. lymphadenopathy, hepato-splenic syndrome, hemolytic anemia

D. myocarditis, retinal vasculitis, polyradiculitis

E. meningoencephalitis, vasculitis of the small intestine

2. In SLE lesions of endocardium occurs in the form of:

A subacute bacterial endocarditis

B. parietal fibroplastic eosinophilic endocarditis of Leffler

C. Libman-Sacks endocarditis

D. endocardial fibroelastosis

E. Any of the above

3.Hematologic changes in SLE may be submitted to:

A hemolytic anemia with reticulocytosis

B. leukopenia

C. lymphopenia

D. thrombocytopenia

E. all of the above disorders

4. SLE is characterized by lesions of to the musculoskeletal system in the form of:

A bilateral sacroileitis

B. non-erosive arthritis two or more peripheral joints

C. erosive arthritis of the peripheral joints

D. ankylosing arthritis of the intervertebral joints

E. Arthritis I-x-metacarpophalangeal joints

5.Patient K., 28 years old, complained of the appearance after sun exposure on the face of persistent erythema, pain, swelling, and limitation of motion in the elbow wrist joints. Body temperature in the armpit - 37.60 C. The preliminary diagnosis SLE can be reliably confirmed by the detection of blood:

A rheumatoid factor

B. anti-neutrophil cytotoxic antibodies

C. antinuclear antibodies

D. antibodies topoisomerase-1

E. antistreptolisin-0

6. The patient 35 years old has SLE, with chronic activity of the first degree, clinically manifested photosensitivity and discoid lupus non-erosive arthritis of the knee. The optimal direction of the treatment will be the appointment:

A. GS

B. cytostatics

C. extracorporeal methods

D. aminohinoline drugs

E. NSAIDs

7.A patient 43 years old, suffering from SLE and receiving maintenance therapy with prednisolone rapidly deteriorated. Worried painful dry cough, joint, muscle and abdominal pain. Has a a seizure. On examination - erythema face, cheilitis, stomatitis, swelling of the joints of the hands. Auscultated pleural friction and pericardial rub. On palpation of the abdomen is defined symptom Schetkin-Blumberg. In general, the analysis of blood - anemia, leukopenia, thrombocytopenia, ESR - 60 mm / hour. ANF high titer. The patient should be assigned:

A high-dose corticosteroids
B. SCS in combination with aminohinolons
C. SCS in combination with NSAIDs
D. Corticosteroids in combination with cytostatics
E. pulse therapy with megadoses of corticosteroids and cytotoxic drugs
8. For SLE patients optimal cytostatic is:
A. Cyclophosphamide +
B. metatreksat
C. Azathioprine
D. cyclosporin A
E. mycophenolate mofetil
9. Active lupus nephritis (morphological variant - membranous glomerulonephritis) with a daily proteinuria to 3 g / day combined therapy is:
A. GS and aminohinolines
B. GS and anticoagulants
C. GS and prostaglandin E1
D. Corticosteroids and cytotoxic drugs
E. Corticosteroids and NSAIDs
10. The diagnosis of antiphospholipid syndrome in SLE is confirmed:
A detection of antibodies to Sm-nuclear antigens
B. Detection of antibodies to native DNA
C. Detection LE-cells
D. discovery of the phenomenon of "sockets"
E. false-positive reaction for syphilis

Standard answers: 1-A, 2-C, 3-E, 4-B, 5-C, 6-D, 7-E, 8-A, 9-D, 10-E.

Practical Lessons # 7-8

Topic 4: Systemic vasculitis

Aim: To teach applicants to master the method of examination of patients with Systemic vasculitis. To study probable etiological and predisposing factors, pathogenesis of Systemic vasculitis, main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis, methods of primary and secondary prophylaxis.

Basic definitions:

№	Term	Definition
1.	**Aneurysm**	Is an outward bulging, likened to a bubble or balloon, caused by a localized, abnormal, weak spot on a blood vessel wall. As an aneurysm increases in size, the risk of rupture, which leads to uncontrolled bleeding, increases. Although they may occur in any blood vessel, particularly lethal examples include aneurysms of the Circle of Willis in the brain, aortic aneurysms affecting the thoracic aorta, and abdominal aortic aneurysms.
2.	**Livedo reticularis**	Is a common skin finding consisting of a mottled reticulated vascular pattern that appears as a lace-like purplish discoloration of the skin. The discoloration is caused by reduction in blood flow through the arterioles that supply the cutaneous capillaries, resulting in deoxygenated blood showing as blue discoloration.
3.	**Anti-neutrophil cytoplasmic antibodies**	Are a group of autoantibodies, mainly of the IgG type, against antigens in the cytoplasm of neutrophil granulocytes (the most common type of white blood cell) and monocytes. They are detected as a blood test in a number of autoimmune disorders, but are particularly associated with systemic vasculitis, so called ANCA-associated vasculitides.
4.	**Mononeuritis multiplex**	Is simultaneous or sequential involvement of individual noncontiguous nerve trunks, either partially or completely, evolving over days to years and typically presenting with acute or subacute loss of sensory and motor function of individual nerves. The pattern of involvement is asymmetric, however, as the disease progresses, deficit(s) becomes more confluent and symmetrical.
5.	**Purpura**	Is a condition of red or purple discolored spots on the skin that do not blanch on applying pressure. The spots are caused by bleeding underneath the skin secondary to platelet disorders, vascular disorders, coagulation disorders, or other causes. They measure 3–10 mm, whereas petechiae measure less than 3 mm, and ecchymoses greater than 1 cm.

Systemic vasculitis (SV) - a group of diseases related to connective tissue diseases which are based on generalized vascular lesions with inflammation and necrosis of the vascular wall, leading to ischemic changes of organs and tissues. The spectrum of clinical manifestations, course and prognosis of SV determined by the type of vasculitis, type, size and location are involved in the pathological process of vascular lesions and to their specific damages. The incidence of SV ranges from 0.4 to 14 or more cases per 100 thousand population, while the socio-economic value is determined by a distinct buildup in recent years, their prevalence, lesion in young, working-age patients with early disability and high mortality if untreated.

Vasculitis is inflammation of blood vessels, often with ischemia, necrosis, and organ inflammation.Vasculitis can affect any blood vessel—arteries, arterioles, veins, venules, or

capillaries. Clinical manifestations of specific vasculitic disorders are diverse and depend on the size and location of the involved vessels and the degree of the organ dysfunction and inflammation.

Etiology

Vasculitis may be primary or secondary. Primary vasculitis results from an inflammatory response that targets the vessel walls and has no known cause. Secondary vasculitis may be triggered by an infection, a drug, or a toxin or may occur as part of another inflammatory disorder or cancer.

The exact cause of vasculitis isn't fully understood. Some types are related to a person's genetic makeup. Others result from the immune system attacking blood vessel cells by mistake. Possible triggers for this immune system reaction include:

- Infections, such as hepatitis B and hepatitis C
- Blood cancers
- Immune system diseases, such as rheumatoid arthritis, lupus and scleroderma
- Reactions to certain drugs

Risk factors

Vasculitis can happen to anyone. Factors that may increase the risk of certain disorders include:

- Age. Giant cell arteritis rarely occurs before the age of 50, while Kawasaki disease is most common in children younger than 5 years old.
- Family history. Behcet's disease, granulomatosis with polyangiitis and Kawasaki disease sometimes run in families.
- Lifestyle choices. Using cocaine can increase your risk of developing vasculitis. Smoking tobacco, especially if you're a man younger than 45, can increase your risk of Buerger's disease.
- Medications. Vasculitis can sometimes be triggered by medications such as hydralazine, allopurinol, minocycline and propylthiouracil.
- Infections. Having hepatitis B or C can increase your risk of vasculitis.
- Immune disorders. People who have disorders in which their immune systems mistakenly attack their own bodies may be at higher risk of vasculitis. Examples include lupus, rheumatoid arthritis and scleroderma.
- Sex. Giant cell arteritis is much more common in women, while Buerger's disease is more common in men.

Pathophysiology

Histologic description of an affected vessel should include the following:

- A description of vessel wall damage (eg, type and location of inflammatory infiltrate, extent and type of damage, presence or absence of fibrinoid necrosis)

- A description of healing responses (eg, intimal hypertrophy, fibrosis)

Certain features (eg, predominant inflammatory cells, location of inflammation) suggest particular vasculitic processes and may aid in the diagnosis. For example, in many acute lesions, the predominant inflammatory cells are PMNs; in chronic lesions, lymphocytes predominate.

Inflammation may be segmental or involve the entire vessel. At sites of inflammation, varying degrees of cellular inflammation and necrosis or scarring occur in one or more layers of the vessel wall. Inflammation in the media of a muscular artery tends to destroy the internal elastic lamina.

Leukocytoclastic vasculitis is a histopathologic term used to describe findings in small-vessel vasculitis. It refers to breakdown of inflammatory cells that leaves small nuclear fragments (nuclear debris) in and around the vessels. Inflammation is transmural and nongranulomatous. PMNs predominate early; later, lymphocytes predominate. Resolution of the inflammation tends to result in fibrosis and intimal hypertrophy. Intimal hypertrophy or secondary clot formation can narrow the vessel lumen and cause tissue ischemia or necrosis.

Classification

Vasculitic disorders can be classified according to the size of the predominant vessel affected. However, there is often substantial overlap.

Size of Affected Vessels	Disorders	Symptoms and Signs
Large	Behçet syndrome Giant cell arteritis Polymyalgia rheumatica Takayasu arteritis	Limb claudication Unequal BP measurements or unequal pulse strength/absent pulse in the limbs CNS ischemic symptoms (eg, strokes)
Medium	Cutaneous vasculitis Polyarteritis nodosa	Symptoms of tissue infarction in affected organs, such as - Muscles: Myalgias - Nerves: Mononeuritis multiplex - GI tract: Mesenteric ischemia - Kidneys: New-onset hypertension - Skin: Ulcers, nodules, and livedo reticularis
Small	Eosinophilic granulomatosis with polyangiitis (formerly called Churg-Strauss syndrome) Cyroglobulinemic vasculitis Granulomatosis with polyangiitis (formerly called Wegener granulomatosis) Immunoglobulin A–associatedvasculitis (formerly called Henoch-Schönlein purpura) Microscopic polyangiitis Small-vessel cutaneous vasculitis	Symptoms of tissue infarction in affected organs similar to those for medium-sized vessels, except skin lesions more likely to be purpuric

Symptoms and Signs

Size of the affected vessels helps determine clinical presentation.

Regardless of the size of the vessels involved, patients can present with symptoms and signs of systemic inflammation (eg, fever, night sweats, fatigue, anorexia, weight loss, arthralgias, arthritis). Some manifestations are life- or organ-threatening and require immediate treatment. They include alveolar hemorrhage, rapidly progressive glomerulonephritis, mesenteric ischemia, and vision loss in patients with giant cell arteritis. Small- and medium-sized vasculitides often manifest with skin lesions such as palpable purpura, urticaria, ulcers, livedo reticularis, and nodules.

General signs and symptoms of most types of vasculitis include:

- Fever
- Headache
- Fatigue
- Weight loss
- General aches and pains

Other signs and symptoms are related to the parts of the body affected, including:

- Digestive system. If your stomach or intestines are affected, you may experience pain after eating. Ulcers and perforations are possible and may result in blood in the stool.
- Ears. Dizziness, ringing in the ears and abrupt hearing loss may occur.
- Eyes. Vasculitis can make your eyes look red and itch or burn. Giant cell arteritis can cause double vision and temporary or permanent blindness in one or both eyes. This is sometimes the first sign of the disease.
- Hands or feet. Some types of vasculitis can cause numbness or weakness in a hand or foot. The palms of the hands and soles of the feet might swell or harden.
- Lungs. You may develop shortness of breath or even cough up blood if vasculitis affects your lungs.
- Skin. Bleeding under the skin can show up as red spots. Vasculitis can also cause lumps or open sores on your skin.

Complications

Vasculitis complications depend on the type and severity of your condition. Or they may be related to side effects of the prescription medications you use to treat the condition. Complications of vasculitis include:

- Organ damage. Some types of vasculitis can be severe, causing damage to major organs.
- Blood clots and aneurysms. A blood clot may form in a blood vessel, obstructing blood flow. Rarely, vasculitis will cause a blood vessel to weaken and bulge, forming an aneurysm (AN-yoo-riz-um).
- Vision loss or blindness. This is a possible complication of untreated giant cell arteritis.
- Infections. Some of the medications used to treat vasculitis may weaken your immune system. This can make you more prone to infections.

Diagnosis

- Clinical evaluation
- Basic laboratory tests to detect inflammation or organ dysfunction (eg, CBC, ESR or C-reactive protein, serum albumin and total protein, AST and ALT, BUN and creatinine, urinalysis)
- Laboratory tests to diagnose the type of vasculitis (eg, antineutrophil cytoplasmic antibodies [ANCA])
- Laboratory and imaging studies that determine the cause of vasculitis and extent of organ involvement
- Biopsy

Systemic vasculitis is suspected in patients with the following:

- Symptoms or signs suggestive of vasculitis (eg, temporal headache and jaw claudication suggesting giant cell arteritis)
- Ischemic manifestations (eg, ischemic stroke, limb claudication, mesenteric ischemia) out of proportion to a patient's risk factors for atherosclerosis
- Unexplained combinations of symptoms in more than one organ system that are compatible with vasculitis (eg, hypertension, myalgias), particularly when symptoms of a systemic illness are present

Primary vasculitic disorders are diagnosed based on the presence of characteristic symptoms, physical findings, compatible laboratory test results, and exclusion of other causes (ie, secondary vasculitis). Histologic examination is done whenever possible and may point to a particular vasculitic disorder.

Routine laboratory tests are done first. Most results are nonspecific but can help support the diagnosis. Tests usually include CBC, ESR or C-reactive protein, serum albumin and total protein, AST, and ALT. Often, patients present with elevated ESR or C-reactive protein, anemia due to

chronic inflammation, elevated platelets, and low serum albumin. Freshly voided urine must be tested for RBCs, RBC casts, and protein to identify renal involvement. Serum creatinine levels should be checked and monitored. Leukopenia and thrombocytopenia are not typical of vasculitis and suggest an alternate diagnosis.

Detection of ANCA may support the diagnosis of granulomatosis with polyangiitis (GPA—formerly known as Wegener granulomatosis), eosinophilic granulomatosis with polyangiitis (EGPA—formerly known as Churg-Strauss syndrome), or microscopic polyangiitis (sometimes called collectively ANCA-associated vasculitides). Standardized tests for ANCA include immunofluorescence staining and enzyme-linked immunosorbent assay (ELISA). Immunofluorescence staining of ethanol-fixed neutrophils can detect the cytoplasmic pattern of c-ANCA or the perinuclear pattern of p-ANCA. Then ELISA is used to check for antibodies specific for the major autoantigens: proteinase-3 (PR3), which produces the c-ANCA staining pattern, or myeloperoxidase (MPO), which produces the p-ANCA staining pattern seen on ethanol-fixed neutrophils. Because ANCA-associated vasculitides are rare, ANCA testing should be done only when the pretest probability for ANCA-associated vasculitis is at least moderately high.

Other useful laboratory tests include hepatitis B and C serologic testing, serum and urine protein electrophoresis, antinuclear antibody and anti-extractable nuclear antigens panel, testing for the presence of cryoglobulins, and complement levels to diagnose viral vasculitis, cryoglobulinemic vasculitis, lymphoproliferative disorders, or vasculitis secondary to other autoimmune diseases.

Further testing is determined by clinical findings. If indicated based on clinical findings, a chest x-ray should be done to check for infiltrates, but high-resolution noncontrast CT of the chest may be needed to check for subtle findings, such as small nodules or cavities. Bilateral diffuse infiltrates suggest possible alveolar hemorrhage, which requires immediate diagnosis and treatment. Other imaging tests may be required. For example, magnetic resonance angiography of large blood vessels and the aorta is useful for diagnosis and monitoring when such vessels appear affected. If symptoms suggest mononeuritis multiplex, electromyography may be helpful.

Because vasculitic disorders are rare and treatment may have severe adverse effects, tissue biopsy is done to confirm the diagnosis whenever possible. Clinical findings suggest the best site for biopsy. Biopsy results are most likely to be positive if taken from affected lung, skin, and kidney tissue. Blind biopsies of organs without clinical manifestations or laboratory suggestion of involvement have a low likelihood of providing positive results.

Treatment

- Induction of remission for life- or organ-threatening vasculitis with corticosteroids plus **cyclophosphamide** or **rituximab**
- Induction of remission for less severe vasculitis with corticosteroids plus a less potent immunosuppressant (eg, **methotrexate**, **azathioprine**, **mycophenolate mofetil**) or **rituximab**
- Maintenance of remission with **methotrexate**, **azathioprine**, or **rituximab**, plus tapering of corticosteroids

Treatment depends on the etiology and extent and severity of disease. For secondary vasculitic disorders, removing the cause (eg, infection, drug, cancer) can help.

For primary vasculitic disorders, treatment aims to induce and maintain remission. Remission is induced by using cytotoxic immunosuppressants and high-dose corticosteroids, usually for 3 to 6 mo, until remission occurs or disease activity is acceptably reduced. The duration of remission is hard to predict and may depend on the type of vasculitis. For many patients, maintaining remission requires continuation of immunosuppressive therapy with or without a low dose of corticosteroids. During this period, the goal is to eliminate corticosteroids or reduce their dose and to use less potent (and less toxic) immunosuppressants as long as needed.

Induction of remission:

For less severe forms of vasculitis, low doses of corticosteroids and less potent immunosuppressants (eg, **methotrexate**, **azathioprine**, **mycophenolate mofetil**) or **rituximab** may be used.

Severe, rapidly progressive and life- or organ-threatening vasculitis (eg, causing alveolar hemorrhage, rapidly progressive glomerulonephritis, or mesenteric ischemia) is a medical emergency requiring hospital admission and immediate treatment. Treatment typically consists of the following:

Corticosteroids: High-dose corticosteroids (also called pulse corticosteroids) are often prescribed.**Methylprednisolone** 15 mg/kg or 1 g IV once/day for 3 days may be used, followed by 1 mg/kg **prednisone** or **methylprednisolone** po once/day for about 4 wk. The dose is then tapered slowly, as tolerated, usually by 10 mg every week to 40 mg/day, by 5 mg every 2 wk to 20 mg/day, by 2.5 mg every 2 wk to 10 mg/day, and by 1 mg every month from there on until the drug is stopped. Changes in this tapering schedule may be necessary if the patient fails to improve or relapses.

Cyclophosphamide: A dose of 2 mg/kg po once/day is usually recommended for at least 3 mo or until remission occurs. The WBC count must be closely monitored, and the dose must be adjusted to avoid leukopenia. (WBC count should be maintained at > 3500/µL.) Less often, a higher dose IV **cyclophosphamide** regimen of 0.5 to 1 g/m2 at 2- to 4-wk intervals is used. The dose should be reduced in patients with significant renal insufficiency, and WBC counts should be monitored frequently. Patients taking **cyclophosphamide** should also be given prophylactic treatment against *Pneumocystis jirovecii*.

Mesna: Mesna is mixed with IV **cyclophosphamide** to bind acrolein, a product of **cyclophosphamide** degradation that is toxic to the bladder epithelium and can lead to hemorrhagic cystitis and sometimes transitional cell carcinoma of the bladder. Long-term use of **cyclophosphamide** increases the risk of bladder cancer. One milligram of **mesna** is added for each milligram of **cyclophosphamide**. Recurrence of hematuria, especially without casts and dysmorphic red cells, should prompt a referral for urologic evaluation. Cystoscopy and renal imaging should be done to exclude cancer.

Rituximab: Rituximab, a B cell-depleting anti-CD20 monoclonal antibody, has been shown to be noninferior to **cyclophosphamide** in inducing remission of severe ANCA-associated vasculitis. **Rituximab** is given as 375 mg/m^2 IV once/wk for 4 wk. A widely used alternative regimen is two 1000-mg infusions given 2 wk apart.

Remission maintenance:

Corticosteroids are tapered to zero or to the lowest dose that can maintain remission. Usually, weekly **methotrexate** (with folate) or daily **azathioprine** is prescribed to replace **cyclophosphamide** because these drugs have a better adverse effects profile. Periodic IV **rituximab** may also be used to maintain remission. The duration of this treatment varies, from one year to several years, depending on the patient, specific diagnosis, and propensity for relapse. Patients with frequent relapses may need to take immunosuppressants indefinitely.

Long-term use of corticosteroids can have significant adverse effects. Patients who are taking such therapy should be given Ca and vitamin D supplements and bisphosphonates to help prevent or minimize osteoporosis; bone density should be monitored.

Key Points

- Vasculitis can be a primary disorder or secondary to other causes.
- Clinical manifestations can be systemic and/or organ-specific, depending on how vessels are affected.
- Vasculitis tends to affect small-, medium-, or large-sized vessels, each with certain patterns of organ involvement.
- Do blood tests, imaging studies, and tissue biopsy as indicated to determine the cause of vasculitis (including disorders such as infections and cancer) and extent of organ involvement.

- Treat with corticosteroids and immunosuppressants.

Lesson duration: 4 hours

Plan

1. Organizational moment (greetings, checking the audience, the message of the topic, the purpose of the lesson, the motivation of applicants to study the topic).
2. Control of basic knowledge (initial survey with tests of the STEP 2 format – attached, check of workbooks on the topic):
2.1. Requirements for theoretical readiness of applicants to perform practical classes.
Knowledge requirements:

- Definition of Systemic vasculitis
- Current views on the etiology and pathogenesis of Systemic vasculitis
- Classification of Systemic vasculitis
- Clinical presentation of Systemic vasculitis
- Diagnostic of Systemic vasculitis
- Differential diagnostic
- Complications of Systemic vasculitis
- Treatment of Systemic vasculitis
- Prognosis for patients with Systemic vasculitis
- Primary and secondary prophylaxis of Systemic vasculitis

List of didactic units:

- to collect in detail the anamnesis of the disease;
- to conduct a physical examination of the patient, to identify and assess changes in his condition;
- make a plan for additional examination, evaluate its results;
- formulate and substantiate a preliminary and clinical diagnosis of Systemic vasculitis, taking into account the severity of disorders according to the classification, comprehensive assessment of patients;
- assessment of possible complications of Systemic vasculitis;
- evaluation of the results of general clinical examination, laboratory analysis of blood, data of X-rays, CTs, MRIs, ultrasound, etc.

2.2. Questions (tests, tasks, clinical cases) to test basic knowledge on the topic of the lesson:

The tests with standard answers.

1. In the development of the inflammation processes glucocorticoids reduce the level of certain most important active enzyme. It results also in the reducing of the synthesis of prostaglandins and leucotrienes which have a key role in the development of inflammation processes. What is the exact name of this enzyme?

A Phospholipase A2
B Arachidonic acid
C Lipoxygenase
D Cyclooxygenase – 1
E Cyclooxygenase – 2

2. A 32-year-old patient has a 3-year history of asthma attacks, that can be hardly stopped with berotec. Over a few last months he has experienced pain in the joints and sensitivity disorder of legs and feet skin. Ps - 80/min, AP - 210/100 mm Hg. In blood: eosinophilia at the rate of 15\%. What disease can be suspected in this case?

A Dermatomyositis
B Systemic lupus erythematosus
C Systemic scleroderma

D Periarteritis nodosa
E Wegener's disease

3. A 16 y.o. female presents with abdominal pain and purpuric spots on the skin. Laboratory investigations reveals a normal platelet count, with haematuria and proteinuria.The most likely diagnosis:

A Haemolytic uraemic syndrome
B Schonlein-Henoch purpura
C Thrombotic thrombocytopenic purpura
D Heavy metal poisoning
E Sub acute bacterial endocarditis

Standard answers: 1-A, 2-D, 3-B.

Clinical case with standards answers:

Patient T., female, aged 22. She felt ill about 7 months ago: there were pains in the large joints, subfebrile body temperature, increasing ESR to 38 mm / hour. Was treated due to reactive arthritis, received penicillin and other drugs. After 6 months began increase weakness, there were dizziness, headache, a sharp decline in visual acuity in the left eye. Internist revealed the weakening of the pulse in the left radial artery, increasing blood pressure. Sent to the hospital.

At admission: state relatively satisfactory. Leather moderately pale, clean. Peripheral lymph nodes were not enlarged. Joints are not changed, the movement in them in full volume. Lungs: pulmonary percussion sound is clear, vesicular breathing, no wheezing. RR - 18 per minute. Left border of heart on the mid-clavicular line, auscultated systolic murmur on all points of auscultation of the heart, the vessels of the neck, the abdominal aorta. Greatly reduced pulsation in the left radial artery. BP on the right hand - 230/130 mm Hg, on the left - 150/130 mm Hg, on her feet - 220/110 mm Hg. Abdomen soft, smooth in all departments. Liver on the edge of the costal arch.

CBC: Er. - 4,8 $x10^{12}$ / l, Hb - 139 g / l, CI - 0,86, L - 5,4 $x10^{9}$ / l, b - 0% e - 3%, bun - 1%, s - 60%, lymph. - 29%, mon. - 7%, ESR - 51 mm / hour.

Urinalysis: a transparent, acid, 1018, protein - 0,33 g / l, no sugar, L. - 0-1-3 in f/v. E. -1-3 in f/v. Fasting glucose 4,23 mmol / l, PTI - 95%. CRP - 2, serum iron - 25 mmol / l, protein - 79 g / l, albumin - 53%, γ- glob. - 19%, fibrinogen - 3,34, cholesterol - 4.5 mmol / l, bilirubin - 12.4 micromol / l.

Ultrasonography of the internal organs: the liver was not enlarged, vessels and ducts are not dilated, the gallbladder is free, the wall is not thickened, pancreas smooth contours, duct did not expand, the kidneys: pyelocaliceal system is not enlarge, parenchyma is preserved.

Ophtalmologist consultation: optic disk grayish-pink color with blurred outlines (swelling of the disks). Retinal artery narrowed sharply and unevenly, sometimes with intermittent gleam, their walls thickened. Vienna convoluted. In the maculae retina thickened, unevenly pigmented. Some small atrophic foci in place resorbed hemorrhage.

Questions:

1. Primary diagnosis?
2. Additional investigation?
3. Differential diagnosis?
4. Treatment?

Answering standards

1. Nonspecific aortoarteriitis with lesions of the aortic arch and its branches, sub-acute course, the 2 degrees of activity.

2. The plan further tests: complete blood count, blood at Wasserman, serological tests for syphilis, total urine test, ECG, aortography, Doppler aorta and its branches, Echo.

3. Syphilitic aortitis, hypertrophic cardiomyopathy, rheumatic fever, active phase.

4. The treatment: steroids, NSAID

III. Formation of professional skills, abilities (mastering the skills of curation, determining the treatment regimen):

1.1. Content of tasks:

Recommendations for tasks: (professional algorithms):

Work at the patient's bedside (according to the algorithm of communication between students and patients).

When examining patients, students must follow the following communication algorithms:

Collection of complaints and anamnesis in patients with internal diseases

1. Friendly facial expression, smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Collection of complaints and medical history of the patient.
5. Explanation of survey results.
6. Explanation of actions (hospitalization, conducting certain examinations) that are planned to be performed in the future.
7. End the conversation.

Physical methods of examination of patients with internal diseases

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Explain to the patient which examination will be performed and obtain his consent.
6. Warning about the possibility of unpleasant feelings during the examination.
7. Preparation for the examination (clean warm hands, trimmed nails, warm phonendoscope, if necessary - use a screen).
8. Conducting an examination (demonstration of clinical skills).
9. Explanation of survey results.
10. End the conversation.

Reporting the results of the examination to patients with internal diseases.

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the results of a particular examination.
5. Involve the patient in the interview (compare the results of this examination with previous results, find out if they understand your explanations).
6. End the conversation.

Planning and forecasting the results of conservative treatment:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the need for prescribed treatment.
5. Involvement of the patient (emphasis on the peculiarities of the drugs, duration of administration, possible side effects; find out whether the patient understands your explanations).
6. End the conversation.

Treatment prognosis message:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the expected results of the prescribed treatment.
5. Involve the patient in the conversation (emphasis on the importance of continuous treatment, adherence to the prescribed treatment regimen, finding out whether your explanations are clear to the patient).
6. End the conversation.

Work 1.

1. Collection of complaints, anamnesis, examination of a patient with acute rheumatic fever.
2. Detection of clinical symptoms.
3. Grouping of symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data (clinical analysis of blood, urine, biochemical analysis of blood, chest X-ray or chest CT-scan, X-ray of joints or MRI or ultrasound of joints, ECG, echocardiography, etc.).
6. Carrying out of the differential diagnosis with other arthritis.
7. Formulation of the clinical diagnosis.
8. Determining the degree of disability.

Work 2.

Appointment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the cathedral library with thematic literature.

The student fills in the protocol of examination of the patient in writing. An example of the initial examination of the patient is attached.

Control materials for the final stage of the lesson:

Tasks for self-control with answers.

CLINICAL CASE #1

Female 65 years old, retired, complaints about the daily rise in temperature, headache. The disease started about a month ago, when there was pain in the muscles of the hips, buttocks, a little later - the muscles of the shoulder girdle, aching pain was quite intense and obstruct the movement (walking, dressing, etc.), almost at the same time began to increase body temperature. CBC: hemoglobin 96 g/l, WBC $11x10^9$, banded 8%, segmented 68%, lymphocytes 16%, monocytes 8%, eosinophils 0%, ESR 65 mm / h; Urinalysis - normal. Chest x-ray: in lungs infiltrative changes are not identified, the heart - hypertrophy of the left ventricle.

Ultrasonography of the abdomen - no change. Administrated voltaren 100 mg / day. Against the background of the treatment of pain in the muscles decreased, body temperature decreased to subfebrile level. But a week ago, develop a strong pain in the left temporal area, only for a short period of relief after receiving additional analgin.

At 50 years of age revealed moderate hypertension (140 and 90 - 160 and 100 mmHg) with rare increases blood pressure to 200 mm and 100 mm Hg. Last 3-4 years - rare retrosternal pain that occurs when walking uphill, climbing stairs. At the age of 30-35 years revealed duodenal ulcer.

On examination: well built, moderately high power, clean skin, peripheral lymph nodes were not enlarged. Joints are not changed. The muscles of the upper and lower extremities of normal size, their strength is not changed, palpation is painful. In the left temporal area visually determined twisted cord (the temporal artery?), The skin over it hyperemic, palpation cord - a tight, sharply painful, not pulsating. Right temporal artery - a soft, painless, pulsating. On the other peripheral vessels pulsation saved. In the lungs, vesicular breathing. Heart: on the top - muted sounds, systolic murmur; on aorta – accentuated II sound and systolic murmur. Pulse 90 bpm, rhythm. BP 160 and 90 mm Hg. Abdomen soft, liver and spleen were not palpable. Kidneys not palpable. Focal neurological symptoms not detected. Vision - within the age norm.

CBC: Er. - 3,3 $x10^{12}$ / l, Hb - 90 g / l, CI - 0,8, L – 9,2 $x10^{9}$ / l, b - 0% e - 0%, ban - 5%, s - 63%, lymph. - 24%, mon. - 8%, ESR - 58 mm / hour. Biochemical analysis of blood: AST 25 units. / L, ALT 30 units. / L, CK 60 units. / L, total protein 78 g/l; albumin 39%, α1-globulins 7%, α2-globulins 15% , β-globulins 12%, γ-globulin 27%. CRP (3 +). Urinalysis - normal. ECG: sinus rhythm, axis deviation to the left, reducing the amplitude of the T V4-V6.

Questions:

1. Primary diagnosis?
2. Treatment?

Answering standards

1. Temporal (giant cell temporal arteriitis, cranial arteritis) cell arteritis or Gorton's disease.
2. Steroids in sufficiently high dosage (prednisolone 40-50 mg / day) for long term.

CLINICAL CASE #2

Patient D. 60 years, male, took tetracycline due to acute respiratory disease. During tetracycline intake noted the appearance of pain and swelling of the knee, hemorrhagic rash legs. After the abolition of drugs and taking antihistamines pain, swelling of joints and rash disappeared. After 2 weeks in connection with a runny nose and subfebrile body temperature independently resumed receiving tetracycline, after which the state has deteriorated- increased body temperature to 38,5 ° C, appeared hemorrhagic discharge rash on the shins, which spread to the thighs and buttocks, there were abdominal pain. Hospitalized with suspected acute appendicitis.

On examination: body temperature 37,1 °. The skin extensor surfaces of legs and feet a small number of hemorrhagic rash. Knee and ankle joints are not deformed, and movement in them a few painful. Chest normal shape, lugs percussion- box sound. Harsh breathing hard, right underscapular region – single buzzing rales. RR – 18 per min. Cardiac sounds are muffled, accentuated II sound on the pulmonary artery. HR - 82, rhythm. BP 150/95 mm Hg. Abdomen soft, slightly painful on palpation. Stool 1-2 times a day without any admixture of blood.

CBC: Hb 90 g / l, leukocytes 17,6$x10^{9}$ / l, banded 9%, ESR 54 mm / h. Urine: 1015, protein 0.9 g / l, 50-60 red blood cells in the field of view, serum creatinine 0.1051 mmol / l. Positive analysis of stool for occult blood. Sputum analysis: eos. 30-40 in f/v.

Radiological findings: were revealed infiltrative changes in lung tissue S5, S6 and right S8, S9 left with a marked increase in vascular pattern. In CT of lungs confirmed the presence of infiltrative changes in lung tissue, and identified syndrome "frosted glass".

Questions:

1. Primary diagnosis?
2. Treatment?

Answering standards

1. Hemorrhagic vasculitis. Relapsing course. Derma-joint-abdomino-nephrotic-pulmonary form. The active phase.
2. Glucocorticoids and cytostatics

CLINICAL CASE #3

Patient L., male, aged 26, complained of intense pain burning character of the lower extremities, predominantly in the feet, violating the patient's sleep and weakness when walking in

the lower extremities, headache, dry mouth, burning tongue, the periodic of pain in epigastric and parumbilical area. Pain in the foot started 6 weeks ago with a sense of numbness and progressed in intensity, spreading up the legs. In fact a long history of recorded work (in the last 6 months) patient in the smokehouse at a meat-packing plants, where it is exposed to lead vapors.

An objective examination: were determined epigastric pain, the liver +3 cm, moderately enlarged inguinal lymph nodes. Laboratory investigation: moderate leucocytosis ($10 \cdot 10^9$ / L), the relative lymphocytopeniya (6%), accelerated ESR (29 mm / h),increasing of transaminases (ALT-3.90 mmmol / l, AST - 1,98 mmol / l), twice received the negative results of a study on the presence of antibodies to HIV. Ultrasound Data: hepatomegaly with a certain extension of the portal vein (diameter - 15 mm) and splenomegaly .

Within the next week the patient's body temperature rose to subfebrile levels, appeared dyspnea during walking, marked increase BP (up to 160/100 mmHg), tachycardia (up to 110-115/min), appeared macule pink skin rash neck and shoulder girdle. The patient was advised Rheumatologist, who also was able to identify anamnestic indication of the loss of 7-8 kg of body weight over the past 2 months, systolic murmur over the entire area of the heart with a maximum on the apex, and muscle pain on palpation. The ECG: signs of left ventricular hypertrophy with systolic overload and myocardial ischemia of anterolateral wall.

Echocariography: a moderate dilatation of the left atrium and left ventricle, mitral and tricuspid regurgitation, concentric hypertrophy of the left ventricular myocardium, a small pericarditis (the thickness of the liquid in the pericardium to 6-7 mm) with intact valvular apparatus. Ejection fraction 62%.

Also noted increased ESR 35 mm / h and CRP - 12 mg / L, lower values of transaminases (ALT - up to 1.3 mmol / l), high levels of circulating immune complexes (309 units. at a rate of up to 100 units.). Spread macule skin rash on the trunk and upper extremities, appeared swollen left forearm and hand with visible subcutaneous venous pattern (with Doppler study showed signs of thrombosis, one superficial veins).

The patient had negative results of rheumatologic serologic tests (rheumatoid factor, LE-phenomenon, antinuclear antibodies, anticardiolipin antibodies).

Questions:

1. Primary diagnosis?
2. Treatment?

Answering standards

1. Given the changing clinical picture of the disease with the appearance of skin rash, myalgia, hypertension, carditis, subfebriliteta against the background of the existing multi mononeyropatii suggest the possibility of the patient's diagnosis of nodular polyarteritis.

2. 3-day combination pulse therapy with methylprednisolone (1000 mg / day) and cyclophosphamide (1000 mg / day 1, therapy). Then, maintenance therapy with methylprednisolone.

CLINICAL CASE #4

Female 46 years old. Transferred to therapeutic department from otolaryngology, which came in late January this year.

December of last year after hypothermia developed rhinitis, and a week later - the pain in right ear and hearing loss. Noted the low subfebrile temperature, the general condition was not violated. Within ten days, took antibiotics, drops in the nose. In a blood test revealed a moderate leukocytosis (9600) and increased ESR (32 mm / hour). In the absence of improvements aimed at the clinic of ENT diseases, where the diagnosis of acute media otitis, right sided purulent sinusitis. Were made bypass the tympanic cavity, puncture of the maxillary cavity, antibiotics. Despite the positive dynamics of otolaryngology, the patient began to deteriorate - the body temperature rose to febrile digits for the first time began to complain of marked malaise, dry cough appeared. The blood analysis revealed: leukocytosis (9600) with band shift (9%), increased ESR to 53 mm / hour, in the

analysis of urine - protein 0.1 g/l, E. 60-70 in f/v. On chest X-ray revealed changes, after which the patient was transferred to therapy department .

On examination: The general condition is satisfactory, the body temperature 37.8°C, clean skin, peripheral lymph nodes were not enlarged, the joints are not changed. RR 20 per minute. Harsh breathing. Cardiac sound loud, murmurs are not listen. BP 120 and 80 mmHg. Pulse 88 bpm. rhythm. Soft abdomen, liver and spleen were not palpable.

CRP (3 +). LE-cells - negative. ANF 1:10. ANCA 1:256 (N: no more than 1:16). RW - negative. Markers of viral hepatitis B and C - not detected.

CT of the chest: At S2 and S6 of the right lung are determined by multiple infiltrates, merging with each other in the root zone, infiltrates have a round shape, with areas of destruction (from 0.5 to 1.5 cm). S6 of the left lung infiltrate similar in diameter to 4.0 cm with small plots of decay. Mediastinal lymph nodes were not enlarged. Fluid in the pleural cavity absent.

Morphological study of biopsy of bronchial mucosa: superficial wall of mucosa with granulomatous tissue, rich in large histiocytes with pale cytoplasm; productive-destructive vasculitis of small vessels.

Questions:

1. Primary diagnosis?
2. Treatment?

Answering standards

1. Diagnosis of Vegener's granulomatosis confirmed by the detection of antibodies to neutrophil cytoplasm (ANCA) in high titer and, most importantly, the morphological changes found in the mucosa of the bronchi (the absence of these changes would require lung biopsy)

2. Glucocorticoid therapy (initial dose of prednisolone 60 mg / day) and cytostatics (cyclophosphamide 150 mg / day), the subsequent maintenance therapy with the same medications.

List of recommended literature source:

Basic:

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8. Chung S.A., Langford C.A., Maz M. et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Antineutrophil Cytoplasmic Antibody–Associated Vasculitis. Arthritis Care & Research Vol. 73, No. 8, August 2021, pp 1088–1105
9. Maz M., Chung S.A., Abril A. et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis. Arthritis Care & Research Vol. 73, No. 8, August 2021, pp 1071–1087
10. Chung S.A., Gorelik M., Langford C.A. et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Polyarteritis Nodosa. Arthritis Care & Research Vol. 73, No. 8, August 2021, pp 1061–1070
11. Rheumatology: Principles and Practice. Ed.by S. Princeton. HAYLE MEDICAL, 2019. 248 p.
12. ABC of Rheumatology, 5th edition. Ed. by A.Adebajo and L.Dunkley. Hoboken, NJ : John Wiley & Sons, Inc., 2018. 209 p.
13. Rheumatology Secrets, 4th edition. Ed.by S.G. West, J. Kolfenbach. Elsevier, 2020. 744 p.

Additional:

3. Kelley and Firestein's Textbook of Rheumatology. 10th ed. / G.S. Firestein, I.B.McInnes et al. – Elsevier Health Sciences, 2017. - 1794 p.
4. Therapeutic Guidelines Rheumatology. – Therapeutic Guidelines Limited, 2017. – 335 p.
5. USMLE Step 2 CK Lecture Notes 2017: Internal Medicine. – Kaplan Inc., 2016. – 473 p.

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European female of 22 years old.

Complaints: weakness, malaise, the presence of brown-cyanotic spots, non-healing wounds on the skin of the legs and feet, swelling in the ankle area, sore throat, pain in the knee joints, depressed mood, an increase in body temperature up to 37.4C.

Medical history: In childhood, she was examined for the presence of erythrocytes in urine, does not remember the details, medical documentation has not been preserved. She considers herself ill for 2 years, when reddish-brown-cyanotic spots appeared on the skin of the legs and feet, not accompanied by any unpleasant sensations. Subsequently, the other complaints described above gradually joined in – weeping painful wounds, swelling appeared. In May 2016 consulted with a dermatologist and was treated with local remedies. At that stage in the analyzes: erythrocyturia (3-5 changed), CBC and rheumatic tests – without features. In June 2016 she was consulted by a rheumatologist and prescribed methylprednisolone with some effect. In the analyzes: positive test for ANCA, weakly positive test for dsDNA, positive for proteinase 3, negative for HBsAg and HCV, biochemistry – no features. CT scan of the lungs – no pathology. MRI of brain – uneven expansion of convexial cerebrospinal fluid spaces; there are no volumetric, focal changes. Doppler of the arteries and veins of the lower extremities – the norm. Skin biopsy at the site of the lesion – nonspecific inflammatory changes. Ultrasound of the kidneys – expansion of single cups of both kidneys. One years ago she started 200 mg cyclophosphamide injections weekly with a positive effect. 6 months ago, swelling appeared on the legs, then weeping wounds appeared again.

Anamnesis of life.

Material and living conditions are satisfactory. Viral hepatitis, tuberculosis, sexually transmitted diseases, HIV denies. Allergic anamnesis is not burdened. There were no occupational hazards. Hereditary history is not burdened. She has not been in contact with infectious patients in the last 3 days.

In childhood, according to the words, she suffered from "toxic-allergic nephropathy", accompanied by some changes in the analysis of urine, at a more mature age, she did not notice any problems with the kidneys.

Insurance history: currently works, has not been on sick leave for the last 12 months.

Condition at admission:

General condition is severe. The position in bed is active. Patient of satisfactory nutrition. BP 130/82 mm Hg Heart rate 74 / min. Borders of relative cardiac dullness are normal. The activity of the heart is rhythmic, the tones are clear. NPV 18 / min. Above the lungs, percussion pulmonary sound. Breathing hard, no wheezing. The tongue is moist and clean. The abdomen is soft, painless on palpation. Liver along the edge of the costal arch. The spleen is not palpable. Pounding along the lumbar region is painless. The ankle joints are swollen. On the lower part of the legs – weeping wounds, partially covered with a fibrous film. Below and above the wounds – brownish-cyanotic areas of the skin of irregular shape 0.5 - 2.0 cm in transverse size, not rising above the surface of the skin.

Preliminary diagnosis:

Polyarthritis nodosa, cutaneous form (ulcerative necrotic lesion of the skin of both legs), with minimal systemic manifestations (erythrocyturia, arthralgia), active phase, severe grade, active stage, activity 2.

Survey plan

- Complete blood count,
- Blood biochemistry, including rheumatic tests, glucose, glucose profile, glycated hemoglobin, kidney function tests, liver enzymes etc.
- Urine analysis,
- ECG,
- Echocardiography

- X-ray of joints, lungs,
- Ultrasound of the kidneys.

Treatment plan

- Bed mode.
- Body temperature control.
- Pentoxiphylline 100 mg / 200 ml i.v. OD
- Methylprednisolone 24 mg orally OD
- Omeprazole 20 mg orally OD
- Pulse-therapy with Methylprednisolone 1000 mg i.v. N3
- Cyclophosphamide 1000 mg i.v. N1

Appendix 2.

Tests of the initial level of knowledge of the KROK format

Topic 4. Systemic vasculitis

1. Patient K., 26 years old. Complained of fatigue, headaches, seizures, dizziness, blurred vision, pain in the large joints of the limbs. Is sick 10 months; notes subfertil temperature, the condition worsened during the last 3-4 weeks. Objectively - t0 - $37,2^0$ C, pale skin. Peripheral lymph nodes are not enlarged. Pulse 84 beats. in 1 min., rhythmic. Dramatically weakened ripple on the left brachial artery. Auscultation - systolic murmur at all points of auscultation, on the vessels of the neck and abdominal aorta. Blood pressure in the left brachial artery - 150/120 mm Hg in the right brachial artery - 220/130 mm Hg and femoral arteries - 220/110 mm Hg Joints of the correct form, painless on palpation, full range of motion. Blood test: Er - 4.8 × 1012 / L, T - 139 g / l, hematocrit - 0.86 L - 5.4 x 109 / l, ESR - 48 mm / hour. Urine analysis - clarity -clear, the reaction - sl. acidic spesific gravity - 1018, Protein - 0.66 g / l, no sugar, red blood cells - 1-2 p / sp, white blood cells - 1-3 p / sp. Establish a preliminary diagnosis:

A. idiopathic dermatomyositis
B. polyarteritis nodosa
C. Noninfection-aortoarteriitis
D. Wegener's granuloma
E. systemic lupus erythematosus

2. Determination of serum ANCA important to diagnose:

A hemorrhagic vasculitis
B. Wegener's granulomatosis
C. nodular polyarteritis
D. Giant cell temporal arteritis
E. all of these vasculitis

3 The patient is 18 years old. with chronic tonsilopharingitis. After the administration of influenza vaccine condition deteriorated: T 38.5^0 C, manifested hemorrhagic skin rush on legs, thighs, buttocks, headache. Takes Paracetamol and loratadine. After 2 days, has manifested sharp cramping pain in the abdomen. He was twice diarrhea mixed with blood. OBJECTIVE: pale, multiple papulo-hemorrhagic rash on umsticks, thighs, buttocks, abdomen. The knee and ankle joints are swollen, painful while Abdominal palpation is painful, there are signs of peritoneal irritation. Preliminary diagnosis:

A nodular polyarteritis
B. acute urticaria
C. atopic dermatitis
D. hemorrhagic vasculitis
E. disease Verlgofa

4. The combination of clinical manifestations of atopic syndrome, including bronchial asthma attacks of expiratory dyspnea, scattered dry rales, listen to auscultation), mono-or polyneuropathy, blood eosinophilia, pulmonary infiltrates detected by X-ray of thorax characteristic:

A. Shenlyayn vasculitis, purpura
B. Charg-Strauss syndrome
C. Horton's disease
D. Wegener's granulomatosis
E. aortoarteritis Takayasu

5. A patient 36 years old, complains of increase body temperature 38.00, myalgia, sweating, decreased sensitivity to pain and weakness in his left leg, pain in the testicles Is sick for about six months, at the beginning of the disease was observed swelling of the small joints of the hands, and therefore received diclofenac Swelling of the joints gradually stoped, but arthralgia saved During the period of illness cheat in weightin OBJECTIVE: pale, the extremities are net changes in skin

pattern, petechial rash type, left foot slightly droops Pulse 90 beats in 1 min., rhythmic BP - 140/95 mm Hg Blood test: HGB - 120 g / l, Er - 4.2 × 1012 / L, L - 11.4 x 109 / l, ESR - 40 mm / hour. Preliminary diagnosis:

A nodular polyarteritis
B. nonspecific aortoarteriit
C. Systemic lupus erythematosus
D. systemic sclerosis
E. Wegener's granuloma

6. For the diagnosis of giant cell arteritis Horton's disease) has a value of palpation of:

A the temporal artery is thick and painful
B. weakening pulse on the brachial artery
C. subcutaneous nodules along the vascular lesions
D. overlooking above the skin purpura
E. palpation study does not provide information

7. Determination of markers of hepatitis B and C is a list of the study for the diagnosis:

A. Wegener's granulomatosis
B. nonspecific aortoarteritis
C. hemorrhagic vasculitis
D. Charj-Strauss syndrome
E. polyarteritis nodosa

8. The optimal combination for induction therapy in systemic necrotizing vasculitis polyarteritis nodosa, Wegener's granulomatosis, Charj-Strauss syndrome) should be considered:

A. Azathioprine and prednisolone
B. leflunomide and prednisolone
C. cyclophosphamide and prednisolone
D. Mycophenolate mofetil and prednisolone
E. Methotrexate and prednisolone

9 Treatment of acute hemorrhagic vasculitis, purpura Shenlyayn besides of the clinical variant should start with the appointment of:

A. pentoxiphilin
B. Heparin
C. Intravenous immunoglobulin
D. prednisolone
E. azathioprine

10. Treatment of giant cell temporal arteritis Horton's disease) should be done using:

A. corticosteroids
B. cytostatics
C. antiplatelet drugs
D. statins
E. all of these medications

Standard answers: 1-C, 2-B, 3-D, 4-B, 5-A, 6-A, 7-E, 8-C, 9-B, 10-E

Practical Lesson #9
Topic 5: Osteoarthritis
Aim: To teach applicants to master the method of examination of patients with Osteoarthritis. To study probable etiological and predisposing factors, pathogenesis of Osteoarthritis, main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis, methods of primary and secondary prophylaxis.
Basic definitions:

№	Term	Definition
1	Osteophytes	Are exostoses (bony projections) that form along joint margins. They should not be confused with enthesophytes, which are bony projections that form at the attachment of a tendon or ligament. Osteophytes are not always distinguished from exostoses in any definite way, although in many cases there are a number of differences. Osteophytes are typically intra-articular (within the joint capsule).
2.	Heberden's nodes	Are hard or bony swellings that can develop in the distal interphalangeal joints.They are a sign of osteoarthritis and are caused by formation of osteophytes. Heberden's nodes are more common in women than in men, and there seems to be a genetic component involved in predisposition to the condition. They are named after William Heberden, an English physician
3.	Bouchard's nodes	Are hard, bony outgrowths or gelatinous cysts on the proximal interphalangeal joints. They are seen in osteoarthritis, where they are caused by formation of calcific spurs of the articular cartilage. Bouchard's nodes are comparable in presentation to Heberden's nodes, but are significantly less common. They are named after French pathologist Charles Jacques Bouchard.
4.	COX-2 inhibitors	Are a type of nonsteroidal anti-inflammatory drug that directly targets cyclooxygenase-2 (COX-2), an enzyme responsible for inflammation and pain. Targeting selectivity for COX-2 reduces the risk of peptic ulceration and is the main feature of celecoxib, rofecoxib, and other members of this drug class.
5.	Replacement arthroplasty	From Greek *arthron*, joint, and *plassein*, to form, or joint replacement surgery, is a procedure of orthopedic surgery in which an arthritic or dysfunctional joint surface is replaced with an orthopedic prosthesis. Joint replacement is considered as a treatment when severe joint pain or dysfunction is not alleviated by less-invasive therapies. It is a form of arthroplasty, and is often indicated from various joint diseases, including osteoarthritis.

Osteoarthritis is the most common form of arthritis, affecting millions of people worldwide. It occurs when the protective cartilage that cushions the ends of the bones wears down over time.

Although osteoarthritis can damage any joint, the disorder most commonly affects joints in your hands, knees, hips and spine.

Osteoarthritis symptoms can usually be managed, although the damage to joints can't be reversed. Staying active, maintaining a healthy weight and receiving certain treatments might slow progression of the disease and help improve pain and joint function.

Etiology

Osteoarthritis occurs when the cartilage that cushions the ends of bones in your joints gradually deteriorates. Cartilage is a firm, slippery tissue that enables nearly frictionless joint motion.

Eventually, if the cartilage wears down completely, bone will rub on bone.

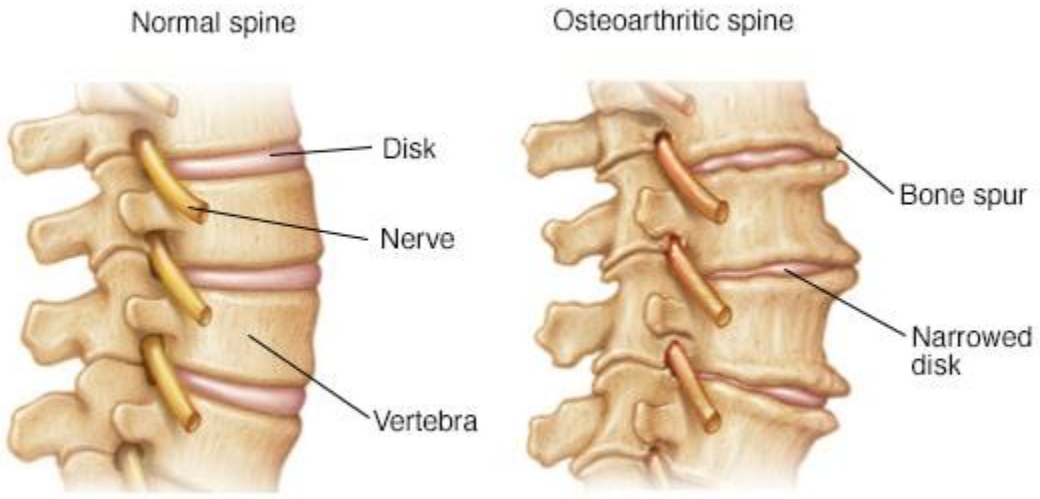
Osteoarthritis has often been referred to as a wear and tear disease. But besides the breakdown of cartilage, osteoarthritis affects the entire joint. It causes changes in the bone and deterioration of the connective tissues that hold the joint together and attach muscle to bone. It also causes inflammation of the joint lining.

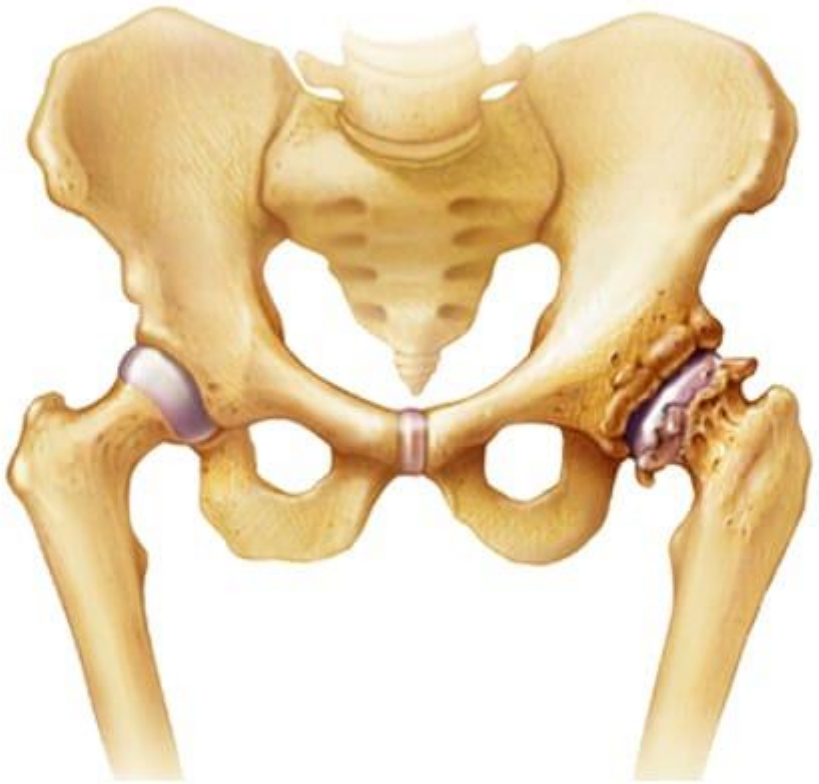
Risk factors

Factors that can increase your risk of osteoarthritis include:

- **Older age.** The risk of osteoarthritis increases with age.
- **Sex.** Women are more likely to develop osteoarthritis, though it isn't clear why.
- **Obesity.** Carrying extra body weight contributes to osteoarthritis in several ways, and the more you weigh, the greater your risk. Increased weight adds stress to weight-bearing joints, such as your hips and knees. Also, fat tissue produces proteins that can cause harmful inflammation in and around your joints.
- **Joint injuries.** Injuries, such as those that occur when playing sports or from an accident, can increase the risk of osteoarthritis. Even injuries that occurred many years ago and seemingly healed can increase your risk of osteoarthritis.
- **Repeated stress on the joint.** If your job or a sport you play places repetitive stress on a joint, that joint might eventually develop osteoarthritis.
- **Genetics.** Some people inherit a tendency to develop osteoarthritis.
- **Bone deformities.** Some people are born with malformed joints or defective cartilage.
- **Certain metabolic diseases.** These include diabetes and a condition in which your body has too much iron (hemochromatosis).

Symptoms





Osteoarthritis symptoms often develop slowly and worsen over time. Signs and symptoms of osteoarthritis include:

- **Pain.** Affected joints might hurt during or after movement.
- **Stiffness.** Joint stiffness might be most noticeable upon awakening or after being inactive.
- **Tenderness.** Your joint might feel tender when you apply light pressure to or near it.
- **Loss of flexibility.** You might not be able to move your joint through its full range of motion.
- **Grating sensation.** You might feel a grating sensation when you use the joint, and you might hear popping or crackling.
- **Bone spurs.** These extra bits of bone, which feel like hard lumps, can form around the affected joint.
- **Swelling.** This might be caused by soft tissue inflammation around the joint.

Complications

Osteoarthritis is a degenerative disease that worsens over time, often resulting in chronic pain. Joint pain and stiffness can become severe enough to make daily tasks difficult.

Depression and sleep disturbances can result from the pain and disability of osteoarthritis.

Diagnosis

During the physical exam, your doctor will check your affected joint for tenderness, swelling, redness and flexibility.

Imaging tests

To get pictures of the affected joint, your doctor might recommend:

- **X-rays.** Cartilage doesn't show up on X-ray images, but cartilage loss is revealed by a narrowing of the space between the bones in your joint. An X-ray can also show bone spurs around a joint.
- **Magnetic resonance imaging (MRI).** An MRI uses radio waves and a strong magnetic field to produce detailed images of bone and soft tissues, including cartilage.

An MRI isn't commonly needed to diagnose osteoarthritis but can help provide more information in complex cases.

Lab tests

Analyzing your blood or joint fluid can help confirm the diagnosis.

- **Blood tests.** Although there's no blood test for osteoarthritis, certain tests can help rule out other causes of joint pain, such as rheumatoid arthritis.
- **Joint fluid analysis.** Your doctor might use a needle to draw fluid from an affected joint. The fluid is then tested for inflammation and to determine whether your pain is caused by gout or an infection rather than osteoarthritis.

Differential diagnosis of OA

	OA	**RA**	**CRYSTAL**
Onset	Gradual	Gradual	Acute
Inflammation?	N	Y	Y
Path	Degenerative	Pannus	Crystal dep.
Type of Joints	Large	Small	Both
Location	DIP & wt. bearing	MCP & wrists	MTP, feet, ankles
Joint deformity's	Bourchard's Heberden's	Ulnar deviation Swan neck Boutaniere	Crystals
X-rays	Osteophytes	Erosions	Erosions
Labs	Nml	(+)	+/-

Treatment

Osteoarthritis can't be reversed, but treatments can reduce pain and help you move better.

Medications

Medications that can help relieve osteoarthritis symptoms, primarily pain, include:

- **Acetaminophen.** Acetaminophen (Tylenol, others) has been shown to help some people with osteoarthritis who have mild to moderate pain. Taking more than the recommended dose of acetaminophen can cause liver damage.
- **Nonsteroidal anti-inflammatory drugs (NSAIDs).** Over-the-counter NSAIDs, such as ibuprofen (Advil, Motrin IB, others) and naproxen sodium (Aleve), taken at the recommended doses, typically relieve osteoarthritis pain. Stronger NSAIDs are available by prescription.

NSAIDs can cause stomach upset, cardiovascular problems, bleeding problems, and liver and kidney damage. NSAIDs as gels, applied to the skin over the affected joint, have fewer side effects and may relieve pain just as well.

- **Duloxetine (Cymbalta).** Normally used as an antidepressant, this medication is also approved to treat chronic pain, including osteoarthritis pain.

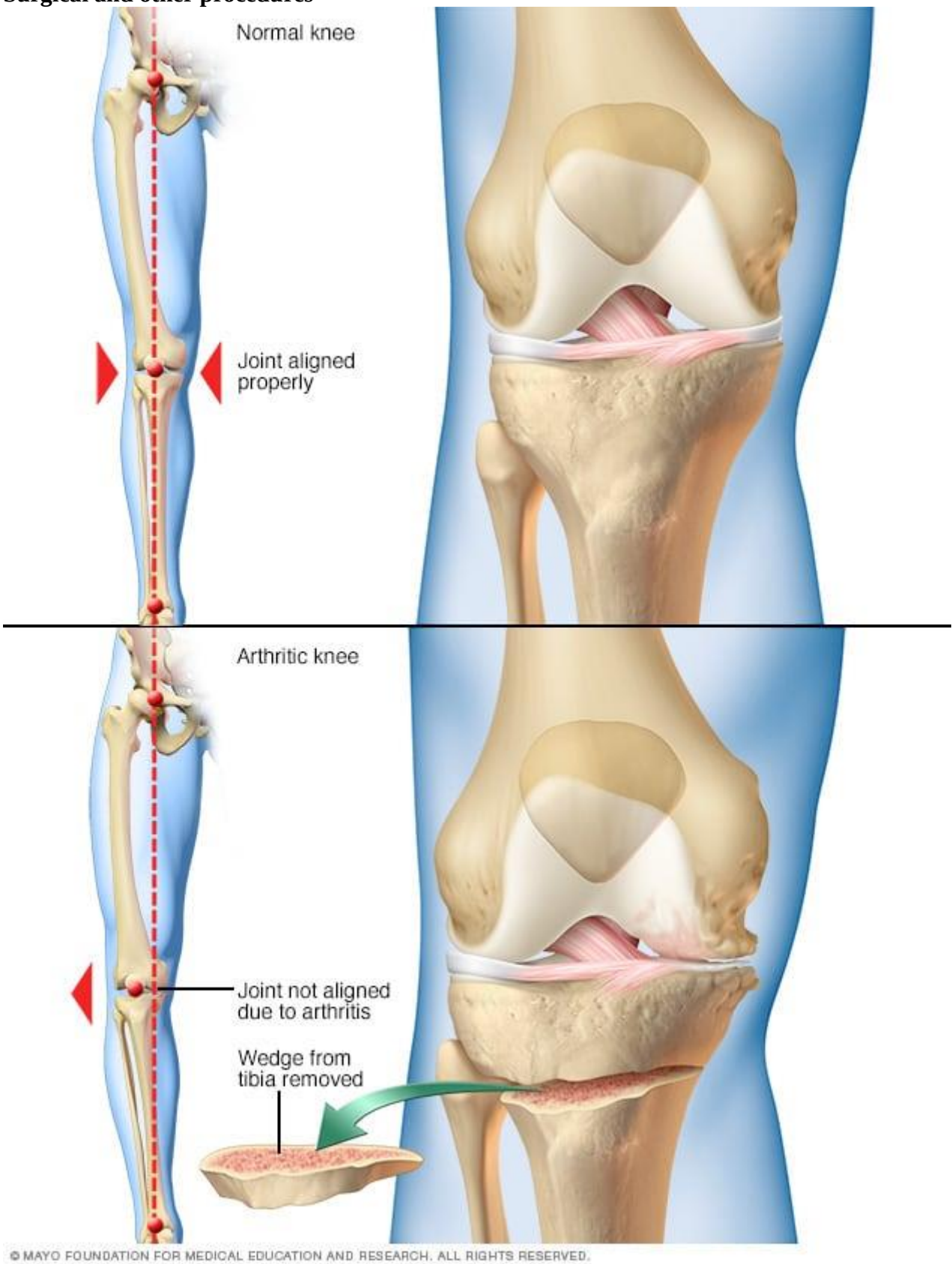
Therapy

- **Physical therapy.** A physical therapist can show you exercises to strengthen the muscles around your joint, increase your flexibility and reduce pain. Regular gentle exercise that you do on your own, such as swimming or walking, can be equally effective.
- **Occupational therapy.** An occupational therapist can help you discover ways to do everyday tasks without putting extra stress on your already painful joint. For instance, a

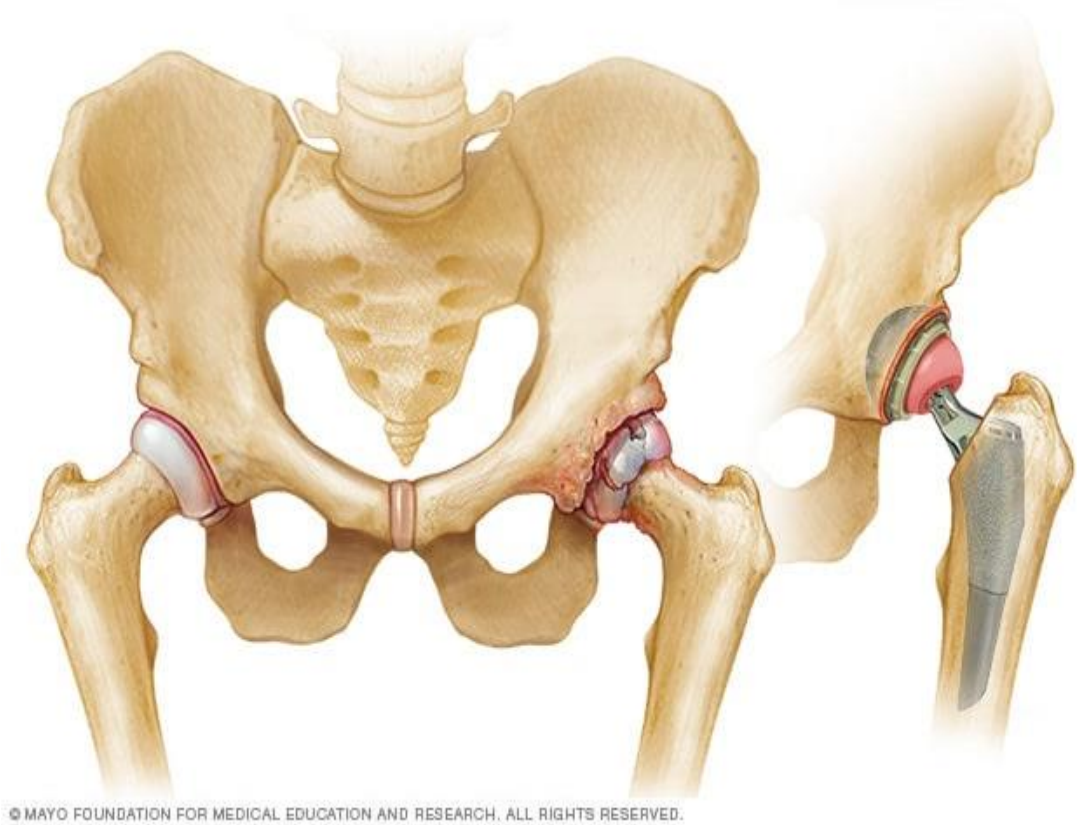
toothbrush with a large grip could make brushing your teeth easier if you have osteoarthritis in your hands. A bench in your shower could help relieve the pain of standing if you have knee osteoarthritis.

- **Transcutaneous electrical nerve stimulation (TENS).** This uses a low-voltage electrical current to relieve pain. It provides short-term relief for some people with knee and hip osteoarthritis.

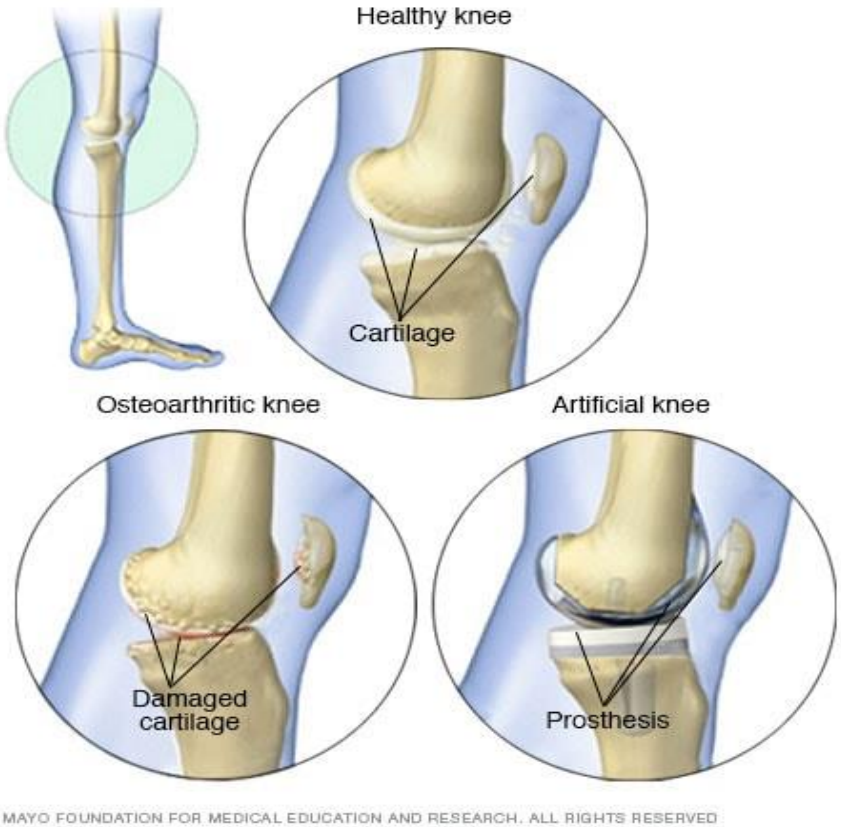
Surgical and other procedures



Knee osteotomyOpen pop-up dialog box



Artificial hipOpen pop-up dialog box

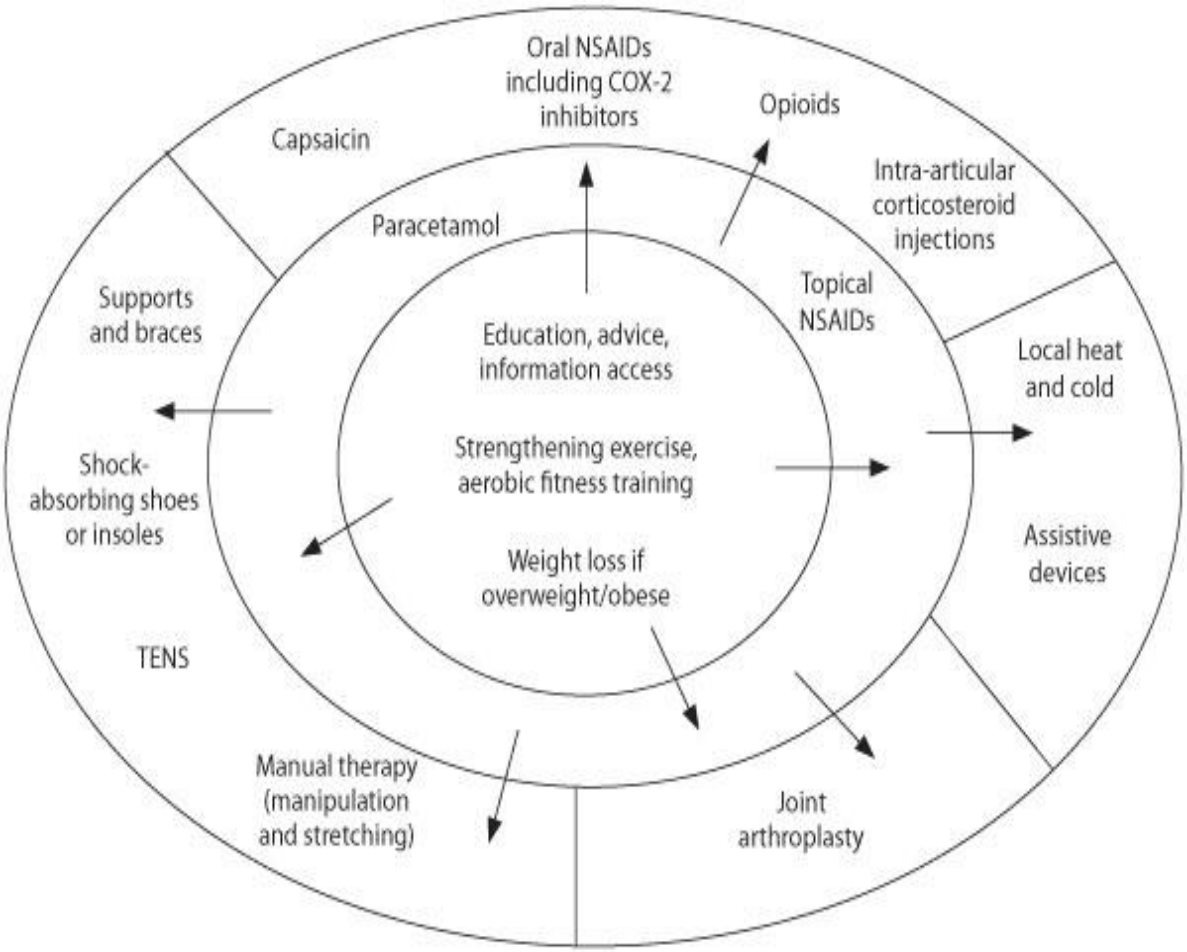


Knee comparisonsOpen pop-up dialog box

If conservative treatments don't help, you might want to consider procedures such as:

- **Cortisone injections.** Injections of a corticosteroid into your joint might relieve pain for a few weeks. Your doctor numbs the area around your joint, then places a needle into the space within your joint and injects medication. The number of cortisone injections you can receive each year is generally limited to three or four, because the medication can worsen joint damage over time.
- **Lubrication injections.** Injections of hyaluronic acid might relieve pain by providing some cushioning in your knee, though some research suggests that these injections offer no more relief than a placebo. Hyaluronic acid is similar to a component normally found in your joint fluid.
- **Realigning bones.** If osteoarthritis has damaged one side of your knee more than the other, an osteotomy might be helpful. In a knee osteotomy, a surgeon cuts across the bone either above or below the knee, and then removes or adds a wedge of bone. This shifts your body weight away from the worn-out part of your knee.
- **Joint replacement.** In joint replacement surgery, your surgeon removes your damaged joint surfaces and replaces them with plastic and metal parts. Surgical risks include infections and blood clots. Artificial joints can wear out or come loose and might eventually need to be replaced.

OA treatment



Lesson duration: 2 hours

Plan

1. Organizational moment (greetings, checking the audience, the message of the topic, the purpose of the lesson, the motivation of applicants to study the topic).
2. Control of basic knowledge (initial survey with tests of the STEP 2 format – attached, check of workbooks on the topic):
2.1. Requirements for theoretical readiness of applicants to perform practical classes.
Knowledge requirements:

- Definition of Osteoarthritis
- Current views on the etiology and pathogenesis of Osteoarthritis
- Classification of Osteoarthritis
- Clinical presentation of Osteoarthritis
- Diagnostic of Osteoarthritis
- Differential diagnostic
- Complications of Osteoarthritis
- Treatment of Osteoarthritis
- Prognosis for patients with Osteoarthritis
- Primary and secondary prophylaxis of Osteoarthritis

List of didactic units:

- to collect in detail the anamnesis of the disease;
- to conduct a physical examination of the patient, to identify and assess changes in his condition;
- make a plan for additional examination, evaluate its results;
- formulate and substantiate a preliminary and clinical diagnosis of Osteoarthritis, taking into account the severity of disorders according to the classification, comprehensive assessment of patients;
- assessment of possible complications of Osteoarthritis;
- evaluation of the results of general clinical examination, laboratory analysis of blood, data of X-rays, CTs, MRIs, ultrasound, etc.

2.2. Questions (tests, tasks, clinical cases) to test basic knowledge on the topic of the lesson:

The tests with standard answers.

1. A 60-year-old male complains of pain in both knees coming on gradually over the past 2 years. The pain is relieved by rest and worsened by the movement. There is bony enlargement of the knees with mild inflammation. Crepitation is noted on motion of the knee joint. There are no other findings except for bony enlargement at the distal interphalangeal joint. The patient is 167 cm tall and weighs 101 kg. The best way to prevent disease progression is

A. **Weight reduction**
B. Calcium supplementation
C. Total knee replacement
D. Aspirin
E. Oral prednisone

2. A 72-year-old man complains of painful joints in his hips and knees, which you have diagnosed as osteoarthritis. Which of the following is the best agent to prescribe for this patient?

A. Naproxen sodium
B. Celecoxib
C. Oral prednisone
D. Intra-articular prednisone
E. Acetaminophen

3. A 58-year-old woman has pain and stiffness in her hands that increases throughout the day. Physical examination shows bony enlargement of the distal interphalangeal joints. X-rays of the hands show joint space narrowing with subchondral sclerosis.

A. Ankylosing spondylitis
B. Fibromyalgia
C. Gonococcal arthritis
D. Gout
E. **Osteoarthritis**

4. A patient 50 y.old, having super nutrition, alcohol abusing, complains of periodical pain in knee and hip joints. Pain increases at walking, flexion of legs. No changes from internal organs revealed. Indicate the most probable diagnosis:

A. Bechterew's disease.
B. Osteoarthritis/
C. Rheumatoid joint inflammation.
D. Gouty arthritis.
E. Rheumatic arthritis.

5. A patient 66 y.old, complains of pains in knee joints at descent down the stairs. Except this, is disturbed by pains in distal parts of fingers, mainly at motion. During examination there are indurations and deformation in finger phalanxes. Indicate the preliminary diagnosis of a patient

A. Osteoarthritis deformans.
B. Gout arthritis.
C. Rheumatic arthritis.
D. Bechterew's disease.
E. Reactive arthritis.

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

Clinical case with standards answers:

The patient, 58 years old, overweight. Complains of pain in the knee joints, aggravated by walking, particularly on stairs . Ill about 7 years. Last 10 days indicated moderate redness of the skin in the area of the knee, swelling, more pronounced dysfunction. OBJECTIVE. Knee joints are deformed, swollen, active and passive movements of the joints is limited by pain, mild muscle atrophy. Uric acid levels are not elevated. In blood indicated a slight leukocytosis, elevated ESR 18 mm/h. Radiological: joint space narrowing in 2-3 times, subchondral sclerosis, osteophytes expressed .

Questions.

1. To formulate the diagnosis.
2. Identify plan of treatment.

Standards of answers .

1 Primary osteoarthritis of the knee, acute phase, II stage, UJF -II.

2.Plan of treatment.

1) Anti-inflammatory and analgesic agents (Olfen 3.0 ml / m 2 twice daily , 10 days , followed by a decrease to maintenance dose with a positive clinical effect).

2) Topical application of ointments and gels with NSAIDs (fastum gel Feld gel) .

3) chondroprotectors (Structum 750 mg 2 times a day for 3 weeks , then 500 mg 2 times daily , long-term).

4) Antioxidants and agents, improving microcirculation (pentoxifylline, ahapurin , dipyridamole).

5) Physio- therapy (phonophoresis with hydrocortisone , magnetic therapy, laser therapy), exercise.

III. Formation of professional skills, abilities (mastering the skills of curation, determining the treatment regimen):

1.1. Content of tasks:

Recommendations for tasks: (professional algorithms):

Work at the patient's bedside (according to the algorithm of communication between applicants and patients).

When examining patients, students must follow the following communication algorithms:

Collection of complaints and anamnesis in patients with internal diseases

1. Friendly facial expression, smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Collection of complaints and medical history of the patient.
5. Explanation of survey results.
6. Explanation of actions (hospitalization, conducting certain examinations) that are planned to be performed in the future.
7. End the conversation.

Physical methods of examination of patients with internal diseases

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Explain to the patient which examination will be performed and obtain his consent.
6. Warning about the possibility of unpleasant feelings during the examination.
7. Preparation for the examination (clean warm hands, trimmed nails, warm phonendoscope, if necessary - use a screen).
8. Conducting an examination (demonstration of clinical skills).
9. Explanation of survey results.
10. End the conversation.

Reporting the results of the examination to patients with internal diseases.

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the results of a particular examination.
5. Involve the patient in the interview (compare the results of this examination with previous results, find out if they understand your explanations).
6. End the conversation.

Planning and forecasting the results of conservative treatment:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the need for prescribed treatment.
5. Involvement of the patient (emphasis on the peculiarities of the drugs, duration of administration, possible side effects; find out whether the patient understands your explanations).
6. End the conversation.

Treatment prognosis message:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.

3. Greetings and introductions, expression of interest, respect and care.

4. Correct and accessible to the patient's understanding explanation of the expected results of the prescribed treatment.

5. Involve the patient in the conversation (emphasis on the importance of continuous treatment, adherence to the prescribed treatment regimen, finding out whether your explanations are clear to the patient).

6. End the conversation.

Work 1.

1. Collection of complaints, anamnesis, examination of a patient with acute rheumatic fever.

2. Detection of clinical symptoms.

3. Grouping of symptoms into syndromes.

4. Definition of the leading syndrome.

5. Interpretation of laboratory and instrumental data (clinical analysis of blood, urine, biochemical analysis of blood, chest X-ray or chest CT-scan, X-ray of joints or MRI or ultrasound of joints, ECG, echocardiography, etc.).

6. Carrying out of the differential diagnosis with other arthritis.

7. Formulation of the clinical diagnosis.

8. Determining the degree of disability.

Work 2.

Appointment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the cathedral library with thematic literature.

The student fills in the protocol of examination of the patient in writing. An example of the initial examination of the patient is attached.

Control materials for the final stage of the lesson:

Tasks for self-control with answers.

CLINICAL CASE #1

A 60-year-old woman presents complaining of bilateral knee pain on most days of the past few months. The pain was gradual in onset. The pain is over the anterior aspect of the knee and gets worse with walking and going up and down stairs. She complains of stiffness in the morning that lasts for a few minutes and a buckling sensation at times in the right knee. On examination, there is a small effusion, diffuse crepitus, and limited flexion of both knees. Joint tenderness is more prominent over the medial joint line bilaterally. She has a steady but slow gait, slightly favouring the right side.

Questions:

1. Specify the preliminary diagnosis
2. Assign a diagnostic investigations
3. Differential diagnosis
4. Assign treatment

Standards of answers

1. Primary osteoarthritis, oligoarthritis with lesions of the knee, active phase, II stage
2. CBC, biochemistry, X-ray of knee, Ultrasound of knee
3. Rheumatoid arthritis, Gout, Ankylosing spondylitis, Reactive arthritis
4. Treatment:

- NSAIDs (celecoxib 200 mg twice a day orally)
- Chondroprotectors (glucosamine 1500 mg once a day orally)
- Physiotherapy
- Topical NSAIDs

CLINICAL CASE #2

A 55-year-old woman has been complaining of pain and swelling in several fingers of both hands for the past 2 months. She describes morning stiffness lasting for 30 minutes. Her mother tells her that she had a similar condition at the same age. She denies any other joint pain or swelling. On examination, she has tenderness, slight erythema, and swelling in one PIP joint and two DIP joints in each hand. She has squaring at the base of her right thumb (the first carpometacarpal joint). There is no swelling or tenderness in her MCP joints.

Questions:

1. Specify the preliminary diagnosis
2. Differential diagnosis
3. Assign treatment
4. Does patient need physiotherapy?

Standards of answers

1. Primary osteoarthritis, polyarthritis with lesions of the hand joints, active phase, II stage
2. Rheumatoid arthritis, Gout, Ankylosing spondylitis, Reactive arthritis
3. Treatment:
    - NSAIDs (celecoxib 200 mg twice a day orally)
    - Chondroprotectors (glucosamine 1500 mg once a day orally)
    - Topical NSAIDs
4. Yes

List of recommended literature source:

Basic:

14. Nikiphorou E, Santos EJF, Marques A, et al. 2021 EULAR recommendations for the implementation of self-management strategies in patients with inflammatory arthritis. Annals of the Rheumatic Diseases 2021; 80: 1278-1285.
15. Uson J, Rodriguez-García SC, Castellanos-Moreira R, et al. EULAR recommendations for intra-articular therapies. Annals of the Rheumatic Diseases 2021; 80: 1299-1305.
16. Kloppenburg M, Kroon FP, Blanco FJ, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. Annals of the Rheumatic Diseases 2019; 78: 16-24.
17. Kolasinski, S.L., Neogi, T., Hochberg, M.C. et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol, 72: 220-233.
18. Rheumatology: Principles and Practice. Ed.by S. Princeton. HAYLE MEDICAL, 2019. 248 p.
19. ABC of Rheumatology, 5th edition. Ed. by A.Adebajo and L.Dunkley. Hoboken, NJ : John Wiley & Sons, Inc., 2018. 209 p.
20. Rheumatology Secrets, 4th edition. Ed.by S.G. West, J. Kolfenbach. Elsevier, 2020. 744 p.

Additional:

6. Kelley and Firestein's Textbook of Rheumatology. 10th ed. / G.S. Firestein, I.B.McInnes et al. – Elsevier Health Sciences, 2017. - 1794 p.
7. Therapeutic Guidelines Rheumatology. – Therapeutic Guidelines Limited, 2017. – 335 p.
8. USMLE Step 2 CK Lecture Notes 2017: Internal Medicine. – Kaplan Inc., 2016. – 473 p.

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European male of 53 years old.

Complaints: severe pain in the joints, mostly in the knees and small joints of the hands, swelling and deformities of the joints, pain in the lumbosacral spine, weakness, malaise, headaches, swelling of the legs.

Medical history: Considers himself ill for about a year, when pain and swelling of the joints began to bother him. He was hospitalized, as a result of the therapy, the patient's condition improved - joint pains, their swelling, pain in the lumbosacral spine decreased, weakness, malaise, headaches ceased to bother him, laboratory parameters improved. Was discharged in satisfactory condition. However, since mid-January, the above complaints have reappeared and intensified. He applied to the hospital again.

Anamnesis of life. Earlier, blood pressure increased, he took bisoprolol, now it does not rise. Periodically worried about pain in the lower back, received massage courses with a positive effect.

Material and living conditions are satisfactory. Tuberculosis, sexually transmitted diseases, HIV, hepatitis denies. There were no occupational hazards. Hereditary history was unremarkable. He has not been in contact with infectious patients in the last 3 days.

Allergic anamnesis is not burdened.

Physical examination: General condition of moderate severity. Consciousness is clear. Active position. Patient of satisfactory nutrition. BP 120/75 mm Hg Heart rate 74 / min. The boundaries of relative cardiac dullness are expanded to the left +0.5 from the left mid-claviculary line. Heart activity is arrhythmic, the tones are muffled. Breath rate is 18 / min. Above the lungs, percussion pulmonary sound. Breathing hard, no wheezing. Tongue moist, coated with white bloom. Abdomen soft, painless on palpation. Liver +2 cm from the edge of the costal arch. The spleen is not palpable. Pounding along the lumbar region is painless. Palpation of the knee joints is sharply painful. The knee joints are enlarged. Small joints of the hands are deformed, edematous, nodules of Bouchard and Heberden are determined, moderately painful on palpation. No peripheral edema.

Preliminary diagnosis:

Osteoarthritis, polyarthritis with damage of the knee, small joints of the hands, functional insufficiency grade 2.

Osteochondrosis of the lumbosacral spine.

Ischemic heart disease, diffuse cardiosclerosis, extrasystolic arrhythmia, CHF0

Arterial hypertension, stage 2, grade 1.

Survey plan

Survey plan

- Complete blood count,
- Blood biochemistry, including rheumatic tests, glucose, glucose profile, glycated hemoglobin, kidney function tests, liver enzymes etc.
- Urine analysis,
- ECG,
- Echocardiography
- X-ray of joints, lungs,
- Ultrasound of the kidneys.

Treatment plan

Meloxicam 1.5 ml i.m. OD
Glucozamine 3 ml i.m. OD
Paracetamol 1000 mg i.v. OD
Pantoprazole 40 mg i.v. OD
Bisoprolol 5 mg orally OD
Aspirin 100 mg orally OD

Atorvastatin	20	mg	orally	OD

Appendix 2.

Tests of the initial level of knowledge of the KROK format

Topic 5. Osteoarthritis

1. A patient 67 years old, obese, smoking, periodically alcohol abusing, complains of pain in left hip and knee joints. During examination there are no changes revealed. Diagnosis – osteoarthritis. Choose prophylaxis for this patient:
   A. Running.
   B. Profession with a long-lasting walking.
   C. Non-smoking.
   D. Non-taking alcohol.
   E. Body mass lowering.

2. A 60 y.o. patient complains of pain in interphalangeal joints of hands with worsening during working. Objectively: distal and proximal joints of the II-IV fingers are deformated, with Heberden's and Bouchard's nodules, painful, stiff. X-ray of joints: joint spaces are constricted, there are marginal entophytes, subchondral sclerosis. What is the most probable diagnosis?
   A. Reiter's disease
   B. Osteoarthritis
   C. Bechterew's disease
   D. Rheumatic arthritis
   E. Psoriatic arthritis

3. A 58-year-old woman suffer from osteoarthritis of knee joints. For 2 weeks she had been receiving an in-patient medical treatment. She was discharged from the hospital in satisfactory condition with complaints of minor pain after prolonged static work. Local hyperaemia and oedema of joints are absent. What further tactics is the most expedient?
   A. Outpatient treatment
   B. Repeated in-patient treatment
   C. Conducting arthroscopy
   D. Refferral to MSEC
   E. Orthopedist consultation

4. Male 60 years old, builder, complaining of pain in the right knee and hip joints, with worsening after exercise. Ill for the last 5 years. Objectively: Obese. Right knee moderately deformed. On the other organs and systems pathology were not found. WBC - 8.2 $x10^9$ / l, ESR 15 mm / h. Uric Acid - 0.35 mmol/ l. What is the most likely diagnosis?
   A. Osteoarthritis
   B. Reactive arthritis
   C. Gout
   D. Rheumatoid arthritis
   E. Reiter's disease

5. Female 56 years old with body mass 110 kg complained of aching pain in the knee, ankle and hip joints that occurs during motion and at rest, amplifies the evening, when changing weather and during exercise. Body temperature is 36,8^{o}C. Knee joints are deformed; joint palpation is painful. The movements are accompanied by crunching. Which of the following is the most likely diagnosis?
   A. Ankylosing spondiloarthritis
   B. Gouty arthritis
   C. Osteoarthritis
   D. Rheumatoid arthritis
   E. Psoriatic arthritis

6. A patient 60 y.old, has deformation in the area of distal interphalangeal joints of hands. Duration of osteoarthritis deformans: many years. Choose names for the described formations

A. Tophuses.
B. Geberden's nodules.
C. Rheumatoid nodules.
D. Rheumatic nodules.
E. Bushar's nodules.

7. A patient 83 y.old, diagnosed osteoarthritis of knee joints. What additional examination should be prescribed for the confirmation of this diagnosis?

A. General blood analysis.
B. General urine analysis.
C. Blood analysis for uric acid.
D. Acute phase reactions.
E. Radiography of joints.

8. A patient 72 y.old has diagnosis: osteoarthritis of a left hip and both knee joints. For the confirmation of diagnosis an X-ray examination of knee joints is recommended. Choose the most probable radiographical changes.

A. Periarticular osteoarthritis.
B. Non-symmetric narrowing of a joint space.
C. Absence of a joint space.
D. Erosion of joint surfaces.
E. Defects of a bony tissue in the area of a joint.

9. A patient 60 y.old, complains of pains in the right knee joint during walking. Suffer from morning stiffness, pains in the joint after a continuous sitting. On examination the joint isn't changed. Painfulness at palpation detected. A patient has overweight, leads a sedentary life. Choose the most probable disease.

A. Rheumatic arthritis.
B. Rheumatoid joint inflammation.
C. Osteoarthritis.
D. Reactive arthritis.
E. Bechterew's disease.

10. A patient 50 y.old, complains of pains in knee joints at physical load. Pain increases at stair climbing. During examination there are no visible changes. Painfulness in the area of an joint space detected. Diagnosis: osteoarthritis. Choose the treatment, indicated for a patient:

A. Antibiotics, nystatin.
B. NSAID.
C. Glucocorticosteroids.
D. Cytostatic.
E. Antibiotics, nystatin, NAID.

Standard answers: 1-E, 2-B, 3-A, 4-A, 5-C, 6-E, 7-E, 8-B, 9-C, 10-B.

Practical Lesson #10-11

Topic 6: Ankylosing Spondylitis. Reactive arthritis

Aim: To teach applicants to master the method of examination of patients with Ankylosing Spondylitis. To study probable etiological and predisposing factors, pathogenesis of Ankylosing Spondylitis, Reactive arthritis main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis, methods of primary and secondary prophylaxis.

Basic definitions:

№	Term	Definition
1.	Dactylitis	Also known as "sausage digit" is a diffuse swelling of a solitary finger or toe, is a distinctive feature of Ankylosing Spondylitis and other peripheral spondylarthritides but can also be seen in polyarticular gout and sarcoidosis.
2.	Conjunctivitis	Is inflammation of the outermost layer of the white part of the eye and the inner surface of the eyelid. It makes the eye appear pink or reddish. Pain, burning, scratchiness, or itchiness may occur. The affected eye may have increased tears or be "stuck shut" in the morning. Swelling of the white part of the eye may also occur. Conjunctivitis can affect one or both eyes.
3.	Uveitis	Is the inflammation of the uvea, the pigmented layer that lies between the inner retina and the outer fibrous layer composed of the sclera and cornea. Uveitis is described anatomically, by the part of the eye affected, as anterior, intermediate or posterior, from front to back. In the panuveitic form, all parts are involved. The commonest is the anterior form.
4.	Seronegativity	"Seronegative" refers to the fact that these diseases are negative for rheumatoid factor, indicating a different pathophysiological mechanism of disease than is commonly seen in rheumatoid arthritis. Seronegative spondyloarthropathy (or seronegative spondyloarthritis) is a group of diseases involving the axial skeleton and having a negative serostatus.
5.	HLA-B27	Human leukocyte antigen subtypes B*2701-2759 – is a class I surface antigen encoded by the B locus in the major histocompatibility complex on chromosome 6 and presents antigenic peptides (derived from self and non-self antigens) to T cells. HLA-B27 is strongly associated with ankylosing spondylitis and other associated inflammatory diseases, such as psoriatic arthritis, inflammatory bowel disease, and reactive arthritis

Ankylosing spondylitis (AS) is a systemic disorder characterized by inflammation of the axial skeleton, large peripheral joints, and digits; nocturnal back pain; back stiffness; accentuated kyphosis; constitutional symptoms; aortitis; cardiac conduction abnormalities; and anterior uveitis. Diagnosis requires showing sacroiliitis on x-ray. Treatment is with NSAIDs or tumor necrosis factor antagonists and physical measures that maintain joint flexibility.

AS is 3 times more frequent in men than in women and begins most often between ages 20 and 40. It is 10 to 20 times more common among 1st-degree relatives of AS patients than in the general population. The risk of AS in 1st-degree relatives with the HLA-B27 allele is about 20%. Increased prevalence of HLA-B27 in whites or HLA-B7 in blacks supports a genetic predisposition. However, the concordance rate in identical twins is only about 50%, suggesting that environmental factors contribute. The pathophysiology probably involves immune-mediated inflammation.

Symptoms and Signs

The most frequent manifestation is back pain, but disease can begin in peripheral joints, especially in children and women, and rarely with acute iridocyclitis (iritis or anterior uveitis). Other early symptoms and signs are diminished chest expansion from diffuse costovertebral involvement, low-grade fever, fatigue, anorexia, weight loss, and anemia.

Back pain—often nocturnal and of varying intensity—eventually becomes recurrent. Morning stiffness, typically relieved by activity, and paraspinal muscle spasm develop. A flexed or bent-over posture eases back pain and paraspinal muscle spasm; thus, kyphosis is common in untreated patients. Severe hip arthritis can eventually develop. In late stages, the patient has accentuated kyphosis, loss of lumbar lordosis, and fixed bent-forward posturing, with compromised pulmonary function and inability to lie flat. There may be peripheral potentially deforming joint involvement, sometimes involving the digits (dactylitis). Achilles and patellar tendinitis can occur.

Systemic manifestations occur in one third of patients. Recurrent, acute anterior uveitis is common and usually responds to local therapy; less commonly it becomes protracted and severe enough to impair vision. Neurologic signs occasionally result from compression radiculitis or sciatica, vertebral fracture or subluxation, or cauda equina syndrome. Cardiovascular manifestations can include aortic insufficiency, aortitis, angina, pericarditis, and cardiac conduction abnormalities (which may be asymptomatic). Dyspnea, cough, or hemoptysis can rarely result from nontuberculous fibrosis or cavitation of an upper lobe of the lung; cavitary lesions can become secondarily infected with Aspergillus. Rarely, AS results in secondary amyloidosis. Subcutaneous nodules do not develop.

Diagnosis

- Lumbosacral spine imaging
- Blood tests (ESR, C-reactive protein, and CBC) or explicit clinical criteria (modified New York criteria)

AS should be suspected in patients, particularly young men, with nocturnal back pain and kyphosis, diminished chest expansion, Achilles or patellar tendinitis, or unexplained anterior uveitis. A 1st-degree relative with AS should heighten suspicion. Patients should generally be tested with ESR, C-reactive protein, and CBC. Rheumatoid factor (RF) and antinuclear antibodies are needed only if peripheral arthritis suggests other diagnoses. No laboratory test is diagnostic, but results can increase suspicion for the disorder or rule out other disorders than can simulate AS. If, after these tests, AS is still suspected, patients should undergo imaging of the lumbosacral spine; demonstration of sacroiliitis on x-ray strongly supports the diagnosis.

Alternatively, AS can be diagnosed by the **modified New York criteria**. Using these criteria, the patient must have imaging study evidence of sacroiliitis and one of the following:

- Restriction of lumbar spinal motion in both the sagittal (looking from the side) and frontal (looking from the back) planes
- Restriction of chest expansion, adjusted for age
- A history of inflammatory back pain

Historical features that distinguish inflammatory back pain from noninflammatory back pain include onset at ≤ 40 yr, gradual onset, morning stiffness, improvement with activity, and duration ≥ 3 mo before seeking medical attention.

ESR and other acute-phase reactants (eg, C-reactive protein) are inconsistently elevated in patients with active AS. Tests for RF and antinuclear antibodies are negative. The HLA-B27 genetic marker is not usually helpful because positive and negative predictive values are low.

The earliest x-ray abnormalities are pseudowidening caused by subchondral erosions, followed by sclerosis or later narrowing and eventually fusion in the sacroiliac joints. Changes are symmetric. Early changes in the spine are upper lumbar vertebral squaring with sclerosis at the corners; spotty ligamentous calcification; and one or two evolving syndesmophytes. Late changes result in a “bamboo spine” appearance, resulting from prominent syndesmophytes, diffuse paraspinal ligamentous calcification, and osteoporosis; these changes develop in some patients on average over 10 yr.

Changes typical of AS may not become visible on plain x-rays for years. CT and MRI show changes earlier, but there is no consensus regarding their role in routine diagnosis.

A herniated intervertebral disk can cause back pain and radiculopathy similar to AS, but the pain is limited to the spine, usually causes more sudden symptoms, and causes no systemic manifestations or laboratory test abnormalities. If necessary, CT or MRI can differentiate it from AS. Involvement of a single sacroiliac joint suggests a different spondyloarthropathy, possibly infection. Tuberculous spondylitis can simulate AS.

Diffuse idiopathic skeletal hyperostosis (DISH) occurs primarily in men > 50 yr and may resemble AS clinically and on x-ray. Patients uncommonly have spinal pain, stiffness, and insidious loss of motion. X-ray findings in DISH include large ossifications anterior to spinal ligaments (the calcification appears as if someone poured candle wax in front and on the sides of the vertebrae), bridging several vertebrae and usually starting at the lower thoracic spine, eventually affecting the cervical and lumbar spine. There is often subperiosteal bone growth along the pelvic brim and at insertion of tendons (such as the Achilles tendon insertion). However, the anterior spinal ligament is intact and frequently bulging, and sacroiliac and spinal apophyseal joints are not eroded. Additional differentiating features are stiffness that is not accentuated in the morning and a normal ESR.

Prognosis

AS is characterized by mild or moderate flares of active inflammation alternating with periods of little or no inflammation. Proper treatment in most patients results in minimal or no disability and in a full, productive life despite back stiffness. Occasionally, the course is severe and progressive, resulting in pronounced incapacitating deformities.

Treatment

- NSAIDs
- Sulfasalazine, methotrexate, or tumor necrosis factor (TNF) antagonists
- Exercises and supportive measures

The goals of treatment are relieving pain, maintaining joint range of motion, and preventing end-organ damage. Because the condition may cause lung fibrosis, cigarette smoking is discouraged.

NSAIDs reduce pain and suppress joint inflammation and muscle spasm, thereby increasing range of motion, which facilitates exercise and prevents contractures. Most NSAIDs work in AS, and tolerance and toxicity dictate drug choice. The daily dose of NSAIDs should be as low as possible, but maximum doses may be needed with active disease. Drug withdrawal should be attempted only slowly, after systemic and joint signs of active disease have been suppressed for several months.

Sulfasalazine may help reduce peripheral joint symptoms and laboratory markers of inflammation in some patients. Dosage should be started at 500 mg/day and increased by 500 mg/day at 1-wk intervals to 1 to 1.5 g bid maintenance; because acute neutropenia can occur, cell counts must be monitored when initiating therapy or increasing drug dose. Peripheral joint symptoms may also abate with methotrexate.

Systemic corticosteroids, immunosuppressants, and most disease-modifying antirheumatic drugs (DMARDs) have no proven benefit and should generally not be used. TNF-α antagonists (eg,etanercept, infliximab, adalimumab) are often strikingly effective treatments for inflammatory back pain.

For proper posture and joint motion, daily exercise and other supportive measures (eg, postural training, therapeutic exercise) are vital to strengthen muscle groups that oppose the direction of potential deformities (ie, the extensor rather than flexor muscles). Reading while lying prone and pushing up on the elbows or pillows and thus extending the back may help keep the back flexible. Because chest wall motion can be restricted, which impairs lung function, cigarette smoking, which also impairs lung function, is strongly discouraged.

Intra-articular depot corticosteroids may be beneficial, particularly when one or two peripheral joints are more severely inflamed than others, thereby compromising exercise and

rehabilitation. They may also help if systemic drugs are ineffective. Corticosteroids injected into the sacroiliac joints may occasionally help severe sacroiliitis.

For acute uveitis, topical corticosteroids and mydriatics are usually adequate. If severe hip arthritis develops, total hip arthroplasty may lessen pain and improve flexibility dramatically.

Reactive arthritis is an acute spondyloarthropathy that often seems precipitated by an infection, usually genitourinary (GU) or gastrointestinal (GI). Common manifestations include asymmetric arthritis of variable severity that tends to affect the lower extremities, sausage-shaped deformities of fingers or toes or both, constitutional symptoms, enthesitis, tendinitis, and mucocutaneous ulcers, including hyperkeratotic or crusted vesicular lesions (keratoderma blennorrhagicum). Diagnosis is clinical. Treatment involves NSAIDs and sometimes sulfasalazine or immunosuppressants.

Spondyloarthropathy associated with urethritis or cervicitis, conjunctivitis, and mucocutaneous lesions (previously called Reiter syndrome) is one type of reactive arthritis.

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Etiology

Two forms of reactive arthritis are common: sexually transmitted and dysenteric. The sexually transmitted form occurs primarily in men aged 20 to 40. Genital infections with *Chlamydia trachomatis*are most often implicated. Men or women can acquire the dysenteric form after enteric infections, primarily *Shigella, Salmonella, Yersinia,* or *Campylobacter*. Reactive arthritis probably results from joint infection or postinfectious inflammation. Although there is evidence of microbial antigens in the synovium, organisms cannot be cultured from joint fluid.

Epidemiology

The prevalence of the HLA-B27 allele in patients is 63 to 96% vs 6 to 15% in healthy white controls, thus supporting a genetic predisposition.

Reactive arthritis is relatively rare, and the incidence in population-based studies is reported to be 0.6 to 27 per 100,000. Reactive arthritis is more common in adult males in the second and third decades of their life.

About 1-3% of patients with nonspecific urethritis will develop an episode of arthritis. Overall, higher disease activity and worse functional capacity are seen in the lower socioeconomic populations.

Epidemiology

Reactive arthritis is an immune-mediated syndrome triggered by a recent infection. It is hypothesized that T lymphocytes are induced by bacterial fragments such as lipopolysaccharide and nucleic acids when invasive bacteria reach the systemic circulation. These activated cytotoxic-T cells then attack the synovium and other self-antigens through molecular mimicry. This is supported by the evidence of Chlamydia trachomatis and C pneumoniae ribosomal RNA transcripts, enteric bacterial DNA, and bacterial degradation products in the synovial tissue and fluid. It is believed that anti-bacterial cytokine response is also impaired in reactive arthritis, resulting in the decreased elimination of the bacteria. It is, however, unclear why such localization of inflammation occurs.

The prevalence of HLA-B27 in reactive arthritis is estimated at 30% to 50% in patients with reactive arthritis, although values range widely. In hospital-based studies with more severely affected patients, frequencies as high as 60% to 80% have been reported. HLA-B27 should not be used as a diagnostic tool for a diagnosis of acute ReA. The presence of HLA-B27 is believed to potentiate reactive arthritis by presenting bacterial antigens to T cells, altering self-tolerance of the

host immune system, increased TNF-alpha production, promoting the invasion of microbes in the gut, and delayed clearance of causative organisms.

Histopatology

Initially, the dermal histopathological features of reactive arthritis are similar to psoriasis. Examination of the synovial fluid reveals large macrophages, reiter cells with phagocytosed neutrophils, lymphocytes, and plasma cells. Extensive pannus formation is very rare.

Medical history

These symptoms manifest several days to weeks after the initial infection. Diarrhea or other symptoms caused by the offending agents are usually resolved by the time the patient develops arthritis. A detailed history and physical examination to investigate any recent illness such as urethritis, diarrhea, etc., should be performed. ReA can be self-limiting, recurrent, or continuous, and about 20% to 25% of the patients may progress to have chronic articular, ocular, and cardiac complications.

For sexually acquired reactive arthritis, there is a history of sexual intercourse, usually with a new partner, within 3 months of arthritis symptoms. Genital symptoms precede arthritis by about 2 weeks on average. It may include dysuria, discharge, testicular pain in men, and intermenstrual or postcoital bleeding, or deep pelvic pain apart from vaginal discharge in women.

Reactive arthritis is very common in HIV individuals, and hence patients with the new-onset disease must have HIV ruled out. Individuals with HIV who develop reactive arthritis often develop severe psoriasiform dermatitis on the scalp, soles, palms, and flexures.

Symptoms and Signs

Reactive arthritis can range from transient monarticular arthritis to a severe, multisystem disorder. Constitutional symptoms may include fever, fatigue, and weight loss. Arthritis may be mild or severe. Joint involvement is generally asymmetric and oligoarticular or polyarticular, occurring predominantly in the large joints of the lower extremities and in the toes. Back pain may occur, usually with severe disease. Enthesopathy (inflammation at tendinous insertion into bone—eg, plantar fasciitis, digital periostitis, Achilles tendinitis) is common and characteristic. Mucocutaneous lesions—small, transient, relatively painless, superficial ulcers—commonly occur on the oral mucosa, tongue, and glans penis (balanitis circinata). Particularly characteristic are vesicles (sometimes identical to pustular psoriasis) of the palms and soles and around the nails that become hyperkeratotic and form crusts (keratoderma blennorrhagicum). Rarely, cardiovascular complications (eg, aortitis, aortic insufficiency, cardiac conduction defects), pleuritis, and CNS or peripheral nervous system symptoms develop.

Urethritis may develop 7 to 14 days after sexual contact (or occasionally after dysentery); low-grade fever, conjunctivitis, and arthritis develop over the next few weeks. Not all features may occur, so incomplete forms need to be considered. In men, the urethritis is less painful and productive of purulent discharge than acute gonococcal urethritis and may be associated with hemorrhagic cystitis or prostatitis. In women, urethritis and cervicitis may be mild (with dysuria or slight vaginal discharge) or asymptomatic. Conjunctivitis is the most common eye lesion. It usually causes mild eye redness and grittiness, but keratitis and anterior uveitis can develop also, causing eye pain, photophobia, and tearing.

Diagnosis

Physical Exam

- Sausage shaped finger, toe, or heel pain
- Asymmetric oligoarthritis- usually of the lower extremities
- Conjunctivitis or iritis
- Acute diarrhea or cervicitis within 4 weeks of the onset of arthritis
- Urethritis or genital ulcers

Two or more of the above features plus involvement of the skeletal system establishes the diagnosis.

Joint and entheses. Patients typically present with acute onset oligo-arthritis, mainly involving the lower extremities, sacroiliac joint, and the lumbar spine. Not more than 6 large joints

are affected at a time, and the knee and ankle are the most commonly affected. Joint pain is classically nocturnal with early morning stiffness. Involvement is asymmetric and affects the weight-bearing joint. The joints are often warm, painful, and swollen. Tendinitis is a common feature of the disease. About 30% of patients suffer from associated enthesitis in the form of plantar fasciitis or Achilles tendinitis.

Extra-articular manifestations may involve the skeletal system (enthesitis, dactylitis), eye (conjunctivitis, anterior uveitis episcleritis, and keratitis), genitourinary (urethritis, cervicitis, prostatitis, salpingo-oophoritis, cystitis or circinate balanitis), mucosal and skin involvement (mucosal ulcers, keratoderma blennorrhagica and erythema nodosum), cardiac (carditis, aortic, conduction and valvular abnormalities), and nail changes (onycholysis, subungual keratosis, or nail pits) also are seen.

Skin and mucocutaneous changes are common and may include hyperkeratotic skin and erythematous dermatitis. Nail dystrophy is common. Other involvements include pustular psoriasis on the sole (keratoderma blenorrhagica), geographic tongue, circinate balanitis, or oral ulceration.
Eye involvement is common and may include conjunctivitis (30%) or uveitis. In patients with visual symptoms, recognition of uveitis is of paramount importance as it can rapidly lead to visual loss.
Rare cases can involve the cardiovascular system causing conduction abnormalities in early-stage and aortic regurgitation when advanced. Myelopathy, as well as non-specific gastrointestinal features of diarrhea and colitis, can also persist.

Evaluation

Reactive Arthritis falls within the subclass of seronegative spondyloarthropathies that affect the axial skeleton. Other members of that group are Ankylosing spondylitis and Psoriatic arthritis. Joint involvement is oligoarticular and asymmetrical.

American College of Rheumatology came up with diagnostic guidelines for Reactive arthritis in 1999. The criteria were divided into

MAJOR

- Asymmetric oligo or monoarthritis involving lower extremities
- Either enteritis or urethritis symptoms preceding the onset of arthritis by a time interval of 3 days to 6 weeks

MINOR

- Presence of a triggering infection as evidenced by culture positivity
- Presence of persistent synovial involvement

A combination of genitourinary symptoms, metatarsophalangeal joint involvement, elevated C reactive protein, and positive HLA- B27 renders a 69% sensitivity and 93.5% specificity to the diagnosis of reactive arthritis.

Although reactive arthritis is a clinical diagnosis, laboratory tests to detect the offending pathogens to confirm concomitant or preceding infections are usually performed to support the diagnosis. Nucleic acid amplification tests from an early morning urine sample or urogenital swab are utilized to detect Chlamydia trachomatis and Neisseria gonorrhea. Nucleic acid amplification test for Mycoplasma genitalium is also available nowadays and is relevant in men with urethritis. Positive evidence of *Chlamydia* by polymerase chain reaction (PCR) in the joint is probably strongly diagnostic, but the current methods used for the detection of chlamydia in the urine are not validated for diagnostic purposes for synovial samples. Serological testing for *Chlamydia trachomatis* is of limited importance due to serological cross-reactivity between *Chlamydia trachomatis* and *Chlamydia pneumoniae*, inability to distinguish past and present infection by the persistence of antibodies, lower or absent antibody response in lower urinary tract infections. Serological testing is available for *Salmonella*, *Yersinia*, and *Campylobacter* but is not useful in clinical practice. There are also gastrointestinal infections, for example, *Shigella*, in which no reliable serological methods exist. A stool culture may be helpful to detect enteric pathogens.

Certain complications, like uveitis, are important to identify. The slit-lamp exam is helpful to diagnose cells in the anterior chamber in acute iritis. Therefore, the presence of ocular symptoms

in a suspected patient should generate a prompt referral to an ophthalmologist. The usual presentation of uveitis will involve acute pain, photophobia, visual impairment, scleral injection, and hypopyon.

Acute phase reactants such as the erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) may be elevated. Joint aspiration must be performed when possible to rule out other arthritis. Aspiration of the joint is often done to rule out septic arthritis and crystalline arthritis. The findings in synovial fluid are nonspecific and are characteristic of inflammatory arthritis, with elevated leukocyte counts (typically 2000 to 4000 WBC per ml), with neutrophil predominance.

HLA B 27 can be measured as it correlates with the severity of the disease but is not diagnostic. It is also important in the localization of arthritis. Sacroiliitis occurs more commonly in HLA B 27 positive patients.

In a patient from an endemic population, the tuberculin skin test should be performed.

Plain radiographs may reveal nonspecific inflammatory joint findings in the acute phase. Ultrasonography or magnetic resonance imaging (MRI) can be used to diagnose peripheral synovitis, enthesitis, or sacroiliitis. Scintigraphy can reveal the early stages of enthesitis.

Reactive arthritis should be suspected in patients with acute, asymmetric arthritis affecting the large joints of the lower extremities or toes, particularly if there is tendinitis or a history of an antecedent diarrhea or dysuria. Diagnosis is ultimately clinical and requires the typical peripheral arthritis with symptoms of GU or GI infection or one of the other extra-articular features. Because these features may manifest at different times, definitive diagnosis may require several months. Serum and synovial fluid complement levels are high, but these findings are not usually diagnostic and need not be measured.

Disseminated gonococcal infection can closely simulate reactive arthritis. Arthrocentesis may fail to differentiate them, owing to inflammatory characteristics of synovial fluid in both disorders and the difficulty of culturing gonococci from this fluid. Clinical characteristics may help; disseminated gonococcal infection tends to involve upper and lower extremities equally, be more migratory, and not cause back pain, and vesicles tend not to be hyperkeratotic. A positive gonococcal culture from blood or skin lesions helps differentiate the two disorders, but a positive culture from the urethra or cervix does not. If differentiation is still difficult, ceftriaxone may be required for simultaneous diagnosis and treatment.

Psoriatic arthritis can simulate reactive arthritis, causing similar skin lesions, uveitis, and asymmetric arthritis. However, psoriatic arthritis often affects mostly the upper extremities and especially the distal interphalangeal joints, may be abrupt in onset but may also develop gradually, causes less enthesopathy, and tends not to cause mouth ulcers or symptoms of GU or GI infection.

Prognosis

The progression of reactive arthritis is variable, but in most people, the disorder is self-limited, with the resolution of the symptoms occurring by 6 to 18 months. Mortality is very rare today and is usually due to the treatments. In general, causes related to sexually transmitted infections have a worse outcome than those caused by gastrointestinal infections. Despite a cure, recurrences are known to occur in 25 to 50% of cases, especially those who are HLA-B27 positive. Reactivation may signal a new infection or stress. About 20% of patients will have a long-term disease that results in enthesitis and destructive arthritis. Elevation of ESR, lack of response to NSAIDs, and the hip joint involvement usually indicate poor outcomes.

Reactive arthritis usually has a self-limited course, and the symptoms resolve within 3 to 5 months. Symptoms lasting beyond 6 months indicate a chronic element of the disease. Sacroiliitis is the most common chronic joint involvement. Patients who are HLA-B27 positive have a higher risk of recurrence of ReA. 15-30% of patients with ReA can develop long-term arthritis or other joint abnormalities. The presence of hip involvement, unresponsiveness to NSAIDs, and ESR greater than 30 portend a worse outcome.

Complications of ReA include:

- Recurrent arthritis (15 to 50%)
- Chronic arthritis or sacroiliitis

- Ankylosing spondylitis (30 to 50% if the patient is also HLA-B27–positive)
- Urethral stricture
- Aortic root necrosis
- Cataracts
- Cystoid macular edem

Differential Diagnosis

The physician should be able to rule out conditions that present with similar clinical findings. The most common differential diagnosis should include:

- Gonococcal arthritis
- Gouty arthritis
- Still disease
- Septic arthritis
- Rheumatic fever
- Psoriatic arthritis
- Ankylosing spondylitis
- Rheumatoid arthritis
- Immunotherapy/immunization–related arthropathy
- Secondary syphilis
- Tubercular arthritis

Treatment

NSAIDs (eg, indomethacin 25 to 50 mg po tid) usually help relieve symptoms. If induced by infection with *C. trachomatis*, doxycycline 100 mg po bid for up to 3 mo may accelerate recovery, but this is controversial. Sulfasalazine as used to treat RA may also be helpful. If symptoms are severe despite NSAIDs and sulfasalazine, azathioprine or methotrexate may be considered. Systemic corticosteroids have no proven value.

If an infectious agent has been identified as a trigger for reactive arthritis, antimicrobial therapy is strongly recommended, often for a long term of 3 to 6 months. It can significantly shorten the time to remission.https://www.ncbi.nlm.nih.gov/books/NBK499831/ Treatment of the underlying concomitant infection, if present, should be initiated without delay. Patients who do not have an active infection do not benefit from antibiotic therapy.https://www.ncbi.nlm.nih.gov/books/NBK499831/ Vasey et al. reported the results of a double-blinded prospective triple placebo trial in which *Chlamydia*-positive patients by PCR were treated for 6 months with a combination of doxycycline and rifampin or azithromycin and rifampin. The treatment arm achieved statistically significant symptom remission and PCR negativity, although the study was underpowered for the identification of the preferred combination of antibiotics.

The goal of therapy in reactive arthritis is to provide symptomatic relief and prevent chronic complications. Non-steroidal anti-inflammatory drugs are the initial treatment of choice in the acute phase. Intra-articular or local glucocorticoids, as in cases of enthesitis or bursitis, can be used if the patient has mono/oligoarthritis. Mechanical devices like orthotics and insoles can be useful. Systemic use of glucocorticoids is limited to severe polyarthritis, cardiac and ocular manifestations. Disease-modifying antirheumatic drugs (DMARDs), mainly sulphasalazine, are effective in both acute and chronic ReA. Other agents such as methotrexate and azathioprine have shown to be useful in chronic arthritis. They are indicated in patients who have failed Nonsteroidal anti-inflammatory drug (NSAID) therapy. Biologicals such as tumor necrosis factor (TNF) blocking agents (e.g., infliximab and etanercept have been suggested in the treatment of reactive arthritis. However, further studies are needed to determine their definitive indications.

All patients should be urged to become physically active. Strengthening exercises are a key component of long term therapy to prevent muscle wasting.

Reactive arthritis is a multiorgan disorder best managed by a team of healthcare professionals that includes a rheumatologist, ophthalmologist, gastroenterologist, physical therapist, nurse, and pharmacist. While evaluating, general physicians should not shy away from exploring the detailed history of sexual contacts and genital symptoms.

There is no cure for reactive arthritis, and the treatment is supportive. All patients should be encouraged to become physically active, and a physical therapy consult should be obtained.

The pharmacist should educate the patient on the types of drugs used, their benefits, and their side effects. If patients are prescribed steroids, the side effects must be closely monitored, and the drugs tapered as soon as the clinical symptoms subside.

A consult with a dermatologist is recommended to assess skin lesions and recommend treatment.

The key feature is patient education to help improve physical conditioning, function, and quality of life. The patient should participate in regular exercises to improve exercise endurance and prevent joint stiffness. Also, the nurse practitioner should educate the patient about safe sex practices to prevent STDs. Because the disorder can induce anxiety and depression, a mental health nurse should follow these patients and offer counsel.

Finally, all patients with reactive arthritis should follow up with an ophthalmologist since they remain at high risk for visual problems.

The social taboo associated with genitourinary symptoms often becomes a challenge in obtaining a complete and accurate history from patients. Some studies have suggested that appropriate treatment of acute Genitourinary infection with a 3-month course of antibiotics can prevent ReA. However, this is highly controversial.

Similarly, from a physician's perspective, identifying the triad of visual, genitourinary, and arthritis symptoms to a pattern of unifying diagnosis are time-sensitive. It is even more so when acute uveitis or iritis sets in, as they can rapidly progress to permanent loss of visual function if not intervened upon in due time.

Key Points

- Ankylosing spondylitis is a systemic disorder that affects the joints and can cause constitutional symptoms, cardiac symptoms, and anterior uveitis.
- Initial manifestation is usually back pain and stiffness sometimes along with peripheral joint symptoms and/or anterior uveitis.
- Diagnose based on the results of lumbosacral spine imaging, blood tests (ESR, C-reactive protein, and CBC), and/or explicit clinical criteria.
- Use NSAIDs to help reduce symptom severity and improve function.
- Use sulfasalazine, methotrexate, or TNF antagonists to relieve joint symptoms.

Equipment: training room, ultrasound machine, X-ray machine.

Lesson duration: 4 hours

Plan

1. Organizational moment (greetings, checking the audience, the message of the topic, the purpose of the lesson, the motivation of applicants to study the topic).
2. Control of basic knowledge (initial survey with tests of the STEP 2 format – attached, check of workbooks on the topic):

2.1. Requirements for theoretical readiness of applicants to perform practical classes.

Knowledge requirements:

- Definition of Ankylosing Spondylitis, Reactive arthritis
- Current views on the etiology and pathogenesis of Ankylosing Spondylitis, Reactive arthritis
- Classification of Ankylosing Spondylitis, Reactive arthritis
- Clinical presentation of Ankylosing Spondylitis, Reactive arthritis
- Diagnostic of Ankylosing Spondylitis, Reactive arthritis
- Differential diagnostic
- Complications of Ankylosing Spondylitis, Reactive arthritis
- Treatment of Ankylosing Spondylitis, Reactive arthritis
- Prognosis for patients with Ankylosing Spondylitis, Reactive arthritis
- Primary and secondary prophylaxis of Ankylosing Spondylitis, Reactive arthritis

List of didactic units:

- to collect in detail the anamnesis of the disease;
- to conduct a physical examination of the patient, to identify and assess changes in his condition;
- make a plan for additional examination, evaluate its results;
- formulate and substantiate a preliminary and clinical diagnosis of Ankylosing Spondylitis, taking into account the severity of disorders according to the classification, comprehensive assessment of patients;
- assessment of possible complications of Ankylosing Spondylitis;
- evaluation of the results of general clinical examination, laboratory analysis of blood, data of X-rays, CTs, MRIs, ultrasound, etc.

2.2. Questions (tests, tasks, clinical cases) to test basic knowledge on the topic of the lesson:

The tests with standard answers.

1. A 22-year-old male develops the insidious onset of low back pain improved with exercise and worsened by rest. There is no history of diarrhea, conjunctivitis, urethritis, eye problems, or nail changes. On exam the patient has loss of mobility with respect to lumbar flexion and extension. He has a kyphotic posture. A plain film of the spine shows widening and sclerosis of the sacroiliac joints. Some calcification is noted in the anterior spinal ligament. Which of the following best characterizes this patient's disease process?

A. He is most likely to have acute lumbosacral back strain and requires bed rest
B. The patient has a spondyloarthropathy, most likely ankylosing spondylitis
C. The patient is likely to die from pulmonary fibrosis and extrathoracic restrictive lung disease
D. A rheumatoid factor is likely to be positive
E. A colonoscopy is likely to show Crohn's disease

2. A 22-year-old man presents with complaints of low back pain for 3 to 4 months and stiffness of the lumbar area, which worsen with inactivity. He reports difficulty in getting out of bed in the morning and may have to roll out sideways, trying not to flex or rotate the spine to minimize pain. A lumbosacral (LS) spine X-ray film would most likely show which of the following?

A. Degenerative joint disease with spur formation
B. Sacroiliitis with increased sclerosis around the sacroiliac joints
C. Vertebral body destruction with wedge fractures
D. Osteoporosis with compression fractures of L3-L5
E. Diffuse osteonecrosis of the LS spine

3. A 23-year-old man with new-onset back and buttock pain presents to his primary care physician for evaluation. He states he has morning stiffness in his back that resolves over the course of the day. Further testing is negative for rheumatoid factor and positive for HLA-B27 surface antigen. For which of the following conditions is the patient at greatest risk?

A. Aortitis
B. Splenomegaly
C. Thrombocytopenia
D. Uveitis
E. Xerostomia

4. A 35-year-old patient has been admitted to a hospital for pain in the left sternoclavicular and knee joints, lumbar area. The disease has an acute character and is accompanied by fever up to 38ºC. Objectively: the left sternoclavicular and knee joints are swollen and painful. In blood: WBCs - 9,5x10^9/l, ESR - 40 mm/h, CRP - 1,5 mmol/l, fibrinogen - 4,8 g/l, uric acid - 0,28 mmol/l. Culture test of the urethra reveals *Chlamydia*. What is the most likely diagnosis?

A. **Reiter's syndrome**
B. Rheumatic arthritis
C. Gout

D. Bechterew's disease
E. Rheumatoid arthritis

5. A patient 61 y.old, complains of pain in hands. During examination a swelling and moderate painfulness of distal interphalangial joints is detected. Diagnosis: Reuter's disease. What data from past history can help to specify the diagnosis?

A. Conjunctivitis, pericarditis.
B. Urethritis, cystitis, arthritis.
C. Conjunctivitis, urethritis, arthritis.
D. Conjunctivitis, myocarditis.
E. Pericarditis, myocarditis, arthritis.

6. A patient 30 y.old, has a nonspecific ulcerative colitis. During the last month noted pain in the left ankle joint, which increased at walking. During examination the joint is oedematic, painful at palpation. Choose the preliminary diagnosis of this patient

A. Reuter's disease.
B. Bechterew's disease.
C. Goutry arthritis.
D. Osteoarthritis.
E. Reactive arthritis on the background of an intestinal pathology.

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

Clinical case with standards answers:

Male, 26 years old, turned to the clinic about pain in his lower back, buttocks and spine, lasting about 1 year. He complains of morning stiffness, with over 2 hours, which decreases after the various movements and exercises. Six months ago, suffered a sudden episode of pain in his right eye, which was regarded as iritis and docked with eye drops containing steroids. Patient's father had a similar pain in the back. On examination, the joints are not swollen. Tomayer's, Schober's symptoms are positive.

1. Primary diagnosis.
2. List diagnostic criteria of the disease.
3. Plan of investigation.
4. Treatment.

Answering standards

1. Ankylosing spondylitis with systemic manifestations (iritis), the central form.
2. Pain and stiffness in the lumbar spine, with a minimum duration of 3 months, does not decrease at ease pain and stiffness in the thoracic spine, limited mobility of the lumbar spine; limitation of respiratory movements; radiological signs of sacroileitis: symmetric II stage or unilateral III-VI stage.
3. R - graphy sacro-vertebral joints, spine, total blood, urine, rheumatic tests, total protein and protein fractions, HLA B - 27.
4. NSAID (meloxicam - 7, 5 mg); Sulfosalazin t.0, 5 g, № 80 (according to the scheme; 1m per day - 1-week, 2m a day - 2-I week, 3t a day - the third week, 4m a day - Week 4 and beyond)

III. Formation of professional skills, abilities (mastering the skills of curation, determining the treatment regimen):

1.1. Content of tasks:

Recommendations for tasks: (professional algorithms):

Work at the patient's bedside (according to the algorithm of communication between students and patients).

When examining patients, applicants must follow the following communication algorithms:

Collection of complaints and anamnesis in patients with internal diseases

1. Friendly facial expression, smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Collection of complaints and medical history of the patient.
5. Explanation of survey results.
6. Explanation of actions (hospitalization, conducting certain examinations) that are planned to be performed in the future.
7. End the conversation.

Physical methods of examination of patients with internal diseases

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Explain to the patient which examination will be performed and obtain his consent.
6. Warning about the possibility of unpleasant feelings during the examination.
7. Preparation for the examination (clean warm hands, trimmed nails, warm phonendoscope, if necessary - use a screen).
8. Conducting an examination (demonstration of clinical skills).
9. Explanation of survey results.
10. End the conversation.

Reporting the results of the examination to patients with internal diseases.

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the results of a particular examination.
5. Involve the patient in the interview (compare the results of this examination with previous results, find out if they understand your explanations).
6. End the conversation.

Planning and forecasting the results of conservative treatment:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the need for prescribed treatment.
5. Involvement of the patient (emphasis on the peculiarities of the drugs, duration of administration, possible side effects; find out whether the patient understands your explanations).
6. End the conversation.

Treatment prognosis message:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the expected results of the prescribed treatment.
5. Involve the patient in the conversation (emphasis on the importance of continuous treatment, adherence to the prescribed treatment regimen, finding out whether your explanations are clear to the patient).

6. End the conversation.

Work 1.

1. Collection of complaints, anamnesis, examination of a patient.
2. Detection of clinical symptoms.
3. Grouping of symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data (clinical analysis of blood, urine, biochemical analysis of blood, chest X-ray or chest CT-scan, X-ray of joints or MRI or ultrasound of joints, ECG, echocardiography, etc.).
6. Carrying out of the differential diagnosis with other arthritis.
7. Formulation of the clinical diagnosis.
8. Determining the degree of disability.

Work 2.

Appointment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the cathedral library with thematic literature.

The student fills in the protocol of examination of the patient in writing. An example of the initial examination of the patient is attached.

Control materials for the final stage of the lesson:

Task for self-control with answers.

1. A patient, aged 40, has been ill during approximately 8 years, complains of pain in the lumbar part of the spine on physical excertion, in cervical and thoracic part (especially when coughing), pain in the hip and knee joints on the right. On examination: the body is fixed in the forward inclination with head down, gluteal muscles atrophy. Spine X-ray: ribs osteoporosis, longitudinal ligament ossification. What is the most likely diagnosis?

A. Ankylosing spondyloarthritis
B. Tuberculous spondylitis
C. Psoriatic spondyloarthropatia
D. Spondyloarthropatia on the background of Reiter's disease
E. Spread osteochondrosis of the vertebral column

2. A 32-year-old male patient has been suffering from pain in the sacrum and coxofemoral joints, pain and stiffness in the lumbar spine for a year. ESR - 56 mm/h. Roentgenography revealed signs of bilateral sacroileitis. The patient is positive of HLA-B27 antigen. What is the most likely diagnosis?

A. **Ankylosing spondylitis**
B. Coxarthrosis
C. Rheumatoid arthritis
D. Reiter's disease
E. Spondylosis

3. A 21 y.o. man complains of having morning pains in his back for the last three months. The pain can be relieved during the day and after physical exercises. Physical examination revealed reduced mobility in the lumbar part of his spine, increase of muscle tonus in the lumbar area and sluch during moving. X-ray pattern of spine revealed bilateral sclerotic changes in the sacrolumbal part. What test will be the most necessary for confirming a diagnosis?

A. HLA-B27

B. ESR
C. Rheumatoid factor
D. Uric acid in blood plasma
E. Antinuclear antibodies

4. Patient M., 35 years old, addressed a doctor with complaints to pains in lumbar spine, morning stiffness, pains in buttocks, knee and ankle joints. What kind of study should be conducted for the diagnosis verification?

A. X-ray examination of knee joints.
B. X-ray examination of ankle joints.
C. X-ray examination of sacroiliac joints.
D. X-ray examination of a spine.
E. None of them.

5. Patient B., 36 years old, is suspected of having an ankylosing spondylitis. What radiographical sign is compulsory for this disease?

A. Usuration.
B. Osteoporosis.
C. Narrowing of a joint space.
D. Periarticular sclerosis.
E. Sacroiliitis.

6. Patient B., 58 years old, doctor, has been having ankylosing spondylitis for 20 years. At present patient has incompetence of joints of III degree. Patient's prognosis

A. Favorable.
B. Has to change profession.
C. Loss of working capacity.
D. Doubtful.
E. Recovery.

7. During 10 years patient L., 35 years old, has been having Bechterew's disease. What's the danger of this disease?

A. Secondary biliary cirrhosis.
B. Myocardial infarction.
C. Affection of muscles.
D. Ankylosis of joints.
E. Affection of eyes.

8. Patient P., 37 years old, complains of pain in buttocks, increasing after midnight, with irradiation to the rear surface of hips. Periodically felt pain and slight swelling of small joints of hands. During examination there's limitation of spine mobility, decrease of chest expansion. Your preliminary diagnosis?

A. Osteoarthritis.
B. Ankylosing spondylitis.
C. Rheumatoid arthritis.
D. Reactive arthritis.
E. Psoriatic arthritis.

Answers: 1-A, 2-A, 3-A, 4-C, 5-E, 6-C, 7-D, 8-B.

Patient K., 32 years old, male. First became ill 10 years ago, when there were purulent excretion from the urethra, a short-term (within 1 day), conjunctivitis, fever up to 38^0C. After 10 days, joined by back pain, arthritis of the right knee joint. Treated within 10 days of doxycycline, the first day to 0.2 g in the following days to 0.1 grams per day with a positive effect.

Again felt ill a month ago (after a casual sexual relationship), appeared pain during urinating, pussy discharge from the urethra. Self treated within 2 weeks of roxithromycin, the phenomenon of urethritis subsided, but there were pains in the lumbar region with irradiation in the

left leg, pain and swelling I metatarsus-phalangeal and knee joints on the right, right-handed under-heel bursitis, limit the movement due to pain. The blood analysis- ESR 40 mm / h, in urine - leycocituria.

1. Primary clinical diagnosis.
2. Plan of additional investigation
3. Differential diagnosis.
4. Treatment.

Answering standards

1. Reactive (urgenitalny) arthritis (Reiter's disease), II degree of activity, relapsing course.
2. Detection of Chlamydia and other intracellular infections in mucosal scrapings urethra (PCR).
3. -Anti-infective drugs: tetracycline: doxycycline, cps. 0,05 g and 0,1 g, № 10 (in 1 standard), at 0.2 grams per day for 30 days or macrolides: azithromycin (sumamed) 500 mg, № (1-st day-1g/daily, then 0,5 g-1 time a day. and then, within 30 days), with subsequent confirmation of etiologic recovery;

- non-steroidal anti-inflammatory drugs: diclofenac-t.50mg (1m 3 times per day); retard-t.100mg (1m a day), injection-3ml (75mg). № 5 (V / m 1 times per day); Nayz - t.100mg № 20, (at 1m 2 times a day) or meloxicam -7, 5 mg № 20, 3 times a day;
- glucocorticoids in the cavity of the ankle once (kenalog-amp.po1 ml (40mg) - 1ll in / articular; diprospan-amp. On 1ml (2 mg) and 1 ml (5mg) - on a 1 ml / articular.

List of recommended literature source:

Basic:

1. Rheumatology: Principles and Practice. Ed.by S. Princeton. HAYLE MEDICAL, 2019. 248 p.
2. ABC of Rheumatology, 5th edition. Ed. by A.Adebajo and L.Dunkley. Hoboken, NJ : John Wiley & Sons, Inc., 2018. 209 p.
3. Rheumatology Secrets, 4th edition. Ed.by S.G. West, J. Kolfenbach. Elsevier, 2020. 744 p.
4. Jubber A., Moorthy A. Reactive arthritis: a clinical review. J R Coll Physicians Edinb 2021; 51: 288–97.
5. 2019 Update of the American College of Rheumatology/ Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis / M.M. Ward, A.Deodhar, L.S. Gensler et al. // Arthritis Rheumatol. – 2019. – Vol. 71, No. 10. – pp. 1599–1613.
6. 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis / D.Heijde, S.Ramiro, R.Landewé / Ann. Rheum. Dis. – 2017. – Vol.76, No.6. – P.978-991.

Additional:

1. Kelley and Firestein's Textbook of Rheumatology. 10th ed. / G.S. Firestein, I.B.McInnes et al. – Elsevier Health Sciences, 2017. - 1794 p.
2. Therapeutic Guidelines Rheumatology. – Therapeutic Guidelines Limited, 2017. – 335 p.
3. Rheumatology: Principles and Practice. Ed.by S. Princeton. HAYLE MEDICAL, 2019. 248 p.
4. ABC of Rheumatology, 5th edition. Ed. by A.Adebajo and L.Dunkley. Hoboken, NJ : John Wiley & Sons, Inc., 2018. 209 p.
5. Rheumatology Secrets, 4th edition. Ed.by S.G. West, J. Kolfenbach. Elsevier, 2020. 744 p.
6. Jubber A., Moorthy A. Reactive arthritis: a clinical review. J R Coll Physicians Edinb 2021; 51: 288–97.

7. Therapeutic Guidelines Rheumatology. – Therapeutic Guidelines Limited, 2017. – 335 p.

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European female of 39 years old.

Complaints: pain in the right hip joint during movements, morning and initial stiffness in joints and in the spine, difficulty turning the head, swelling of the legs and feet, muscle weakness, general malaise.

Medical history: Joint pain started since 2007. She sought medical help, the condition was regarded as seronegative rheumatoid arthritis, received Lefno® with insufficient effect. In 2013, a study of the sacroiliac joint was performed, changes were identified. She was examined by rheumatologist, diagnosed with ankylosing spondylitis. Subsequently, methotrexate was prescribed, which is still taking. Left knee arthroplasty was performed on August 7, 2018 and on November 14, 2019, enoprosthesis surgery of the right knee joint was performed. Feeling worsened a week ago.

Life history: Long-term suffered from iron deficiency anemia, periodically receiveding iron supplements.

Previously detected subclinical hypothyroidism.

Previously detected lower diaphragm sphincter insufficiency.

There are no bad habits. Infectious diseases denied. There was no blood transfusion. She did not note allergic reactions to drugs.

Physical examination

The general condition of the patient is moderate evere. Consciousness is clear. The position in the bed is forced, the patient is mostly lying down. The skin and visible mucous membranes are pale pink, wrinkles around the mouth, resembling a "purse mouth". When getting up, it does not stretch immediately. Head turns are limited due to stiffness and pain in extreme positions. Nutrition is normal. The thyroid gland is not enlarged. Peripheral lymph nodes are not enlarged. The throat is clean. The tongue is wet, scratched, covered with uneven plaque. At percussion of a thorax a pulmonary sound. Vesicular respiration. Wheezing is not heard. BH 18 breaths. in / min at rest. AT 132/83 mm Hg. Pulse 76 beats / min, rhythmic, satisfactory filling and tension. Limits of relative cardiac dullness: not shifted. Heart tones are rhythmic, muffled, heart rate corresponds to the pulse. The abdomen is painless on palpation in all departments. The liver is enlarged by 1 cm along the mid-clavicular line, sensitive to palpation of the lower edge. The spleen is not palpable. Pasternatsky's symptom is negative on both sides. The pulsation on the vessels of the feet is preserved. The right knee joint is slightly swollen after surgery.

Diagnosis:

Ankylosing spondylitis, HLA-B27-positive, peripheral form, activity of the third degree, bilateral sacroiliitis, spondyloarthritis of the cervical (second degree) and lumbar spine (third degree), right coxarthrosis of the 1st-2nd degree. bilateral gonarthrosis III-IV degree. Condition after arthroplasty of the left knee, right knee.

Mild iron deficiency anemia.

Chronic venous insufficiency of the vessels of the lower extremities 1 degree.

Survey plan:

- Complete blood count,
- Blood biochemistry, including rheumatic tests, glucose, glucose profile, glycated hemoglobin, kidney function tests, liver enzymes etc.
- Urine analysis,
- Stool culture test.
- ECG,
- X-ray of joints, lungs,

Treatment plan:

- Metylprednisolone 8 mg OD orally
- Methotrexate 10 mg once a week orally
- Folic acid 5 mg once a week orally

- Paracetamol 1000 mg OD i.v.
- Meloxicam 1.5 ml OD i.m.
- Iron supplements orally
- Omeprazole 40 mg OD i.v.

Appendix 2.

Tests of the initial level of knowledge of the KROK format

Topic 6. Ankylosing Spondylitis. Reactive arthritis.

1. Patient P., 37 years old, complains of pain in buttocks, increasing after midnight, with irradiation to the rear surface of hips. Periodically felt pain and slight swelling of small joints of hands. During examination there's limitation of spine mobility, decrease of chest expansion. Your preliminary diagnosis?
   A. Osteoarthritis.
   B. Ankylosing spondylitis.
   C. Rheumatoid arthritis.
   D. Reactive arthritis.
   E. Psoriatic arthritis.

2. A 22-year-old man presents with complaints of low back pain for 3 to 4 months and stiffness of the lumbar area, which worsen with inactivity. He reports difficulty in getting out of bed in the morning and may have to roll out sideways, trying not to flex or rotate the spine to minimize pain. A lumbosacral (LS) spine X-ray film would most likely show which of the following?
   A. Degenerative joint disease with spur formation
   B. Sacroiliitis with increased sclerosis around the sacroiliac joints
   C. Vertebral body destruction with wedge fractures
   D. Osteoporosis with compression fractures of L3-L5
   E. Diffuse osteonecrosis of the LS spine

3. A 23-year-old man with new-onset back and buttock pain presents to his primary care physician for evaluation. He states he has morning stiffness in his back that resolves over the course of the day. Further testing is negative for rheumatoid factor and positive for HLA-B27 surface antigen. For which of the following conditions is the patient at greatest risk?
   A. Aortitis
   B. Splenomegaly
   C. Thrombocytopenia
   D. Uveitis
   E. Xerostomia

4. A patient, aged 40, has been ill during approximately 8 years, complains of pain in the lumbar part of the spine on physical excertion, in cervical and thoracic part (especially when coughing), pain in the hip and knee joints on the right. On examination: the body is fixed in the forward inclination with head down, gluteal muscles atrophy. Spine X-ray: ribs osteoporosis, longitudinal ligament ossification. What is the most likely diagnosis?
   A. Ankylosing spondyloarthritis
   B. Tuberculous spondylitis
   C. Psoriatic spondyloarthropatia
   D. Spondyloarthropatia on the background of Reiter's disease
   E. Spread osteochondrosis of the vertebral column

5. A 32-year-old male patient has been suffering from pain in the sacrum and coxofemoral joints, pain and stiffness in the lumbar spine for a year. ESR - 56 mm/h. Roentgenography revealed signs of bilateral sacroileitis. The patient is positive of HLA-B27 antigen. What is the most likely diagnosis?
   A. Ankylosing spondylitis
   B. Coxarthrosis
   C. Rheumatoid arthritis
   D. Reiter's disease
   E. Spondylosis

6. A 21 y.o. man complains of having morning pains in his back for the last three months. The pain

can be relieved during the day and after physical exercises. Physical examination revealed reduced mobility in the lumbar part of his spine, increase of muscle tonus in the lumbar area and sluch during moving. X-ray pattern of spine revealed bilateral sclerotic changes in the sacrolumbal part. What test will be the most necessary for confirming a diagnosis?

A. HLA-B27
B. ESR
C. Rheumatoid factor
D. Uric acid in blood plasma
E. Antinuclear antibodies

7. Patient M., 35 years old, addressed a doctor with complaints to pains in lumbar spine, morning stiffness, pains in buttocks, knee and ankle joints. What kind of study should be conducted for the diagnosis verification?

A. X-ray examination of knee joints.
B. X-ray examination of ankle joints.
C. X-ray examination of sacroiliac joints.
D. X-ray examination of a spine.
E. None of them.

8. Patient B., 36 years old, is suspected of having an ankylosing spondylitis. What radiographical sign is compulsory for this disease?

A. Usuration.
B. Osteoporosis.
C. Narrowing of a joint space.
D. Periarticular sclerosis.
E. Sacroiliitis.

9. Patient B., 58 years old, doctor, has been having ankylosing spondylitis for 20 years. At present patient has incompetence of joints of III degree. Patient's prognosis

A. Favorable.
B. Has to change profession.
C. Loss of working capacity.
D. Doubtful.
E. Recovery.

10. During 10 years patient L., 35 years old, has been having Bechterew's disease. What's the danger of this disease?

A. Secondary biliary cirrhosis.
B. Myocardial infarction.
C. Affection of muscles.
D. Ankylosis of joints.
E. Affection of eyes.

Answers: 1-B, 2-B, 3-D, 4-A, 5-A, 6-A, 7-C, 8-E, 9-C, 10-D.

Practical Lesson #12
Topic 7: Gout
Aim: To teach applicants to master the method of examination of patients with gout. To study probable etiological and predisposing factors, pathogenesis of gout, main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis, methods of primary and secondary prophylaxis.
Basic definitions:

№	Term	Definition
1.	Tophus (plural – Tophi)	Deposits of monosodium urate crystals, in people with longstanding high levels of uric acid in the blood. Tophi are pathognomonic for the gout. Chronic tophaceous gout is known as Harrison Syndrome.
2.	Hyperuricaemia (hyperuricemia)	Abnormally high level of uric acid in the blood. Serum uric acid concentrations greater than 6 mg/dL (360 μmol/l) are defined as hyperuricemia.
3.	Purine	Heterocyclic aromatic organic compound that consists of two rings (pyrimidine and imidazole) fused together. It is water-soluble. Purines are found in high concentration in meat and meat products, especially internal organs such as liver and kidney. In general, plant-based diets are low in purines. Examples of high-purine sources include: sweetbreads, anchovies, sardines, liver, beef kidneys, brains, herring, mackerel, scallops, beer and gravy. Some legumes, including lentils and black eye peas, are considered to be high purine plants.

Gout is precipitation of monosodium urate crystals into tissue, usually in and around joints, most often causing recurrent acute or chronic arthritis. The initial attack of acute arthritis is usually monarticular and often involves the 1st metatarsophalangeal joint. Symptoms include acute pain, tenderness, warmth, redness, and swelling. Diagnosis requires identification of crystals in synovial fluid. Treatment of acute attacks is with anti-inflammatory drugs. The frequency of attacks can be reduced by regular use of NSAIDs, colchicine, or both and by treating hyperuricemia with allopurinol, febuxostat, or uricosuric drugs.

Gout is more common among men than women. Usually, gout develops during middle age in men and after menopause in women. Gout is rare in younger people but is often more severe in people who develop the disorder before age 30. Gout often runs in families.

Pathophysiology

The greater the degree and duration of hyperuricemia, the greater is the likelihood that gout will develop. Urate levels can be elevated because of

- Decreased excretion (most common)
- Increased production
- Increased purine intake

Why only some people with elevated serum uric acid (urate) levels develop gout is not known.

Decreased renal excretion is by far the most common cause of hyperuricemia. It may be hereditary and also occurs in patients receiving diuretics and in those with diseases that decrease GFR. Ethanol increases purine catabolism in the liver and increases the formation of lactic acid, which blocks urate secretion by the renal tubules. Lead poisoning and cyclosporine, usually in the higher doses given to transplant patients, damage renal tubules, leading to urate retention.

Increased production of urate may be caused by increased nucleoprotein turnover in hematologic conditions (eg, lymphoma, leukemia, hemolytic anemia) and in conditions with increased rates of cellular proliferation and cell death (eg, psoriasis, cytotoxic cancer therapy, radiation therapy). Increased urate production may also occur as a primary hereditary abnormality and in obesity, because urate production correlates with body surface area. In most cases, the cause

of urate overproduction is unknown, but a few cases are attributable to enzyme abnormalities; deficiency of hypoxanthine-guanine phosphoribosyltransferase (complete deficiency is Lesch-Nyhan syndrome) is a possible cause, as is overactivity of phosphoribosylpyrophosphate synthetase.

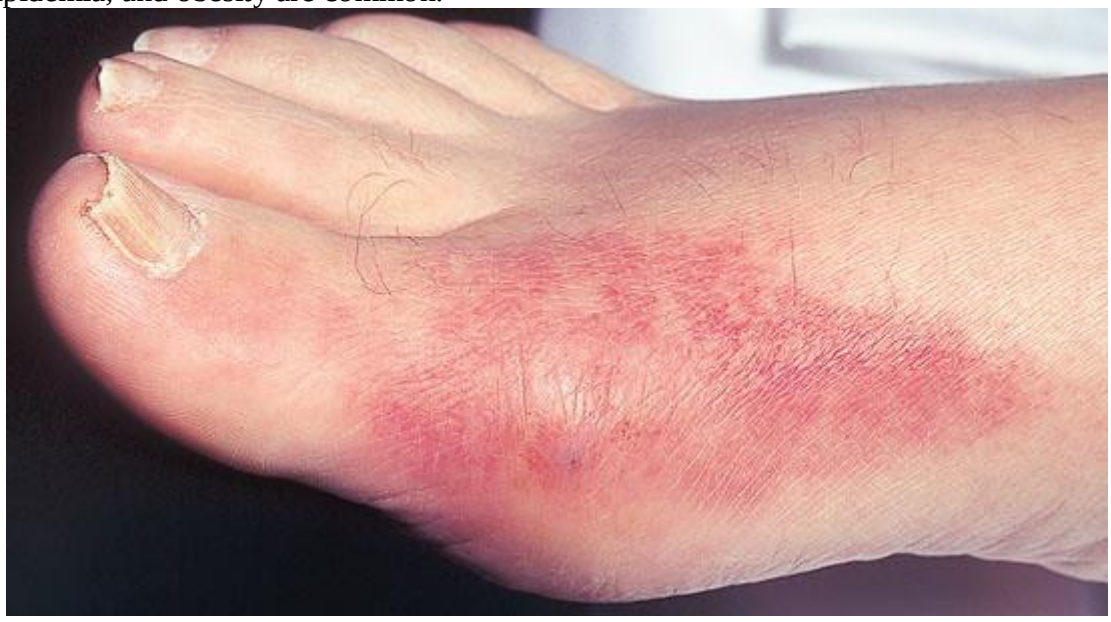
Increased intake of purine-rich foods (eg, liver, kidney, anchovies, asparagus, consommé, herring, meat gravies and broths, mushrooms, mussels, sardines, sweetbreads) can contribute to hyperuricemia. However, a strict low-purine diet lowers serum urate by only about 1 mg/dL.

Urate precipitates as needle-shaped monosodium urate (MSU) crystals, which are deposited extracellularly in avascular tissues (eg, cartilage) or in relatively avascular tissues (eg, tendons, tendon sheaths, ligaments, walls of bursae) and skin around cooler distal joints and tissues (eg, ears). In severe, long-standing hyperuricemia, MSU crystals may be deposited in larger central joints and in the parenchyma of organs such as the kidney. At the acid pH of urine, urate precipitates readily as small platelike or irregular crystals that may aggregate to form gravel or stones, which may obstruct urine outflow. Tophi are MSU crystal aggregates that most often develop in joint and cutaneous tissue.

Acute gouty arthritis may be triggered by trauma, medical stress (eg, pneumonia or other infection), surgery, use of thiazide diuretics or drugs with hypouricemic effects (eg, allopurinol, probenecid, nitroglycerin), or indulgence in purine-rich food or alcohol. Attacks are often precipitated by a sudden increase or, more commonly, a sudden decrease in serum urate levels. Why acute attacks follow some of these precipitating conditions is unknown. Tophi in and around joints can limit motion and cause deformities, called chronic tophaceous gouty arthritis. Chronic gout increases the risk of developing secondary osteoarthritis.

Symptoms and Signs

Acute gouty arthritis usually begins with sudden onset of pain (often nocturnal). The metatarsophalangeal joint of a great toe is most often involved (called podagra), but the instep, ankle, knee, wrist, and elbow are also common sites. Rarely, the hip, shoulder, sacroiliac, sternoclavicular, or cervical spine joints are involved. The pain becomes progressively more severe, usually over a few hours, and is often excruciating. Swelling, warmth, redness, and exquisite tenderness may suggest infection. The overlying skin may become tense, warm, shiny, and red or purplish. Fever, tachycardia, chills, and malaise sometimes occur. Coexisting hypertension, hyperlipidemia, and obesity are common.



Podagra, or acute pain in the 1st metatarsophalangeal joint accompanied by redness, tenderness, and swelling (as seen in this image), is a common manifestation of acute gout.

Course: The first few attacks usually affect only a single joint and last only a few days. Later attacks may affect several joints simultaneously or sequentially and persist up to 3 wk if untreated. Subsequent attacks develop after progressively shorter symptom-free intervals. Eventually, several attacks may occur each year.

Tophi develop most often in patients with chronic gout, but they can rarely occur in patients who have never had acute gouty arthritis. They are usually firm yellow or white papules or nodules, single or multiple. They can develop in various locations, commonly the fingers, hands, feet, and around the olecranon or Achilles tendon. Tophi can also develop in the kidneys and other organs and under the skin on the ears. Patients with osteoarthritic Heberden nodes may develop tophi in the nodes. This development occurs most often in elderly women taking diuretics. Normally painless, tophi, especially in the olecranon bursae, can become acutely inflamed and painful. Tophi may even erupt through the skin, discharging chalky masses of urate crystals. Tophi may eventually cause deformities.

Chronic gout: Chronic gouty arthritis can cause pain, deformity, and limited joint motion. Inflammation can be flaring in some joints while subsiding in others. About 20% of patients with gout develop urolithiasis with uric acid stones or Ca oxalate stones. Complications include obstruction and infection, with secondary tubulointerstitial disease. Untreated progressive renal dysfunction, most often related to coexisting hypertension or, less often, some other cause of nephropathy, further impairs excretion of urate, accelerating crystal deposition in tissues.

Cardiovascular disease and the metabolic syndrome are common among patients with gout.

Diagnosis

- Clinical criteria
- Synovial fluid analysis

Gout should be suspected in patients with acute mono- or oligoarticular arthritis, particularly older adults or those with other risk factors. Podagra and recurrent instep inflammation are particularly suggestive. Previous attacks that began explosively and resolved spontaneously are also characteristic. Similar symptoms can result from the following:

- Ca pyrophosphate dihydrate (CPPD) crystal deposition disease (however, CPPD generally occurs in larger joints, is not associated with tophi, and its clinical course is usually milder)
- Acute rheumatic fever with joint involvement and juvenile idiopathic arthritis (however, these disorders occur mostly in young people, who rarely get gout)
- RA (however, in RA, all affected joints flare, persist in flares for longer, and subside together, whereas in gout, inflammation is usually flaring in some joints while subsiding in others)
- Acute fracture in patients unable to provide a history of injury
- Infectious arthritis (differentiation requires synovial fluid analysis)
- Palindromic rheumatism
- Acute calcific periarthritis caused by basic Ca phosphate and Ca oxalate crystal deposition diseases

Palindromic rheumatism is characterized by acute, recurrent attacks of inflammation in or near one or occasionally several joints with spontaneous resolution; pain and erythema can be as severe as in gout. Attacks subside spontaneously and completely in 1 to 3 days. Such attacks may herald the onset of RA, and rheumatoid factor tests can help in differentiation; they are positive in about 50% of patients (these tests are positive in 10% of gouty patients also).

Synovial fluid analysis: If acute gouty arthritis is suspected, arthrocentesis and synovial fluid analysis should be done at the initial presentation. A typical recurrence in a patient with known gout does not mandate arthrocentesis, but it should be done if there is any question of the diagnosis or if the patient's risk factors or any clinical characteristics suggest infectious arthritis. Synovial fluid analysis can confirm the diagnosis by identifying needle-shaped, strongly negatively birefringent urate crystals that are free in the fluid or engulfed by phagocytes. Synovial fluid during attacks has inflammatory, usually 2,000 to 100,000 WBCs/μL, with > 80% polymorphonuclear WBCs. These findings overlap considerably with infectious arthritis, which must be excluded by Gram stain and culture.

Serum urate level: An elevated serum urate level supports the diagnosis of gout but is neither specific nor sensitive; at least 30% of patients have a normal serum urate level during an acute attack. However, the serum urate level reflects the size of the extracellular miscible urate pool. The level should be measured on 2 or 3 occasions in patients with newly proven gout to establish a baseline; if elevated (> 7 mg/dL [> 0.41 mmol/L]), 24-h urinary urate excretion can also be measured. Normal 24-h excretion in people eating a regular diet is about 600 to 900 mg. Quantification of urinary uric acid can indicate whether hyperuricemia results from impaired excretion or increased production and is useful if a uricosuric drug is used for urate-lowering therapy. Patients with elevated urine excretion of urate are at increased risk of urolithiasis and uricosuric drugs are typically avoided.

X-rays of the affected joint may be taken to look for bony tophi but are probably unnecessary if the diagnosis has been established by synovial fluid analysis. In CPPD, radiopaque deposits are present in fibrocartilage, hyaline articular cartilage (particularly the knee), or both.

Diagnosis of chronic gouty arthritis:

Chronic gouty arthritis should be suspected in patients with persistent joint disease or subcutaneous or bony tophi. Plain x-rays of the 1st metatarsophalangeal joint or other affected joint may be useful. These x-rays may show punched-out lesions of subchondral bone with overhanging bony margins, most commonly in the 1st metatarsophalangeal joint; lesions must be ≥ 5 mm in diameter to be visible on x-ray. Joint space is typically preserved until very late in the course of disease.

Bone lesions are not specific or diagnostic but nearly always precede the appearance of subcutaneous tophi.

Diagnostic ultrasonography is increasingly used to detect a typical double-contour sign suggesting urate crystal deposition, but sensitivity is operator-dependent.

Prognosis

With early diagnosis, therapy enables most patients to live a normal life. For many patients with advanced disease, aggressive lowering of the serum urate level can resolve tophi and improve joint function. Gout is generally more severe in patients whose initial symptoms appear before age 30. The high prevalence of metabolic syndrome and cardiovascular disease probably increases mortality in patients with gout.

Some patients do not improve sufficiently with treatment. The usual reasons include nonadherence, alcoholism, and undertreatment by physicians.

Treatment

Treatment of acute attacks:

NSAIDs are effective in treating acute attacks and are generally well tolerated. However, they can cause adverse effects, including GI upset or bleeding, hyperkalemia, increases in creatinine, and fluid retention. Elderly and dehydrated patients are at particular risk, especially if there is a history of renal disease. Virtually any NSAID used in anti-inflammatory (high) doses is effective and is likely to exert an analgesic effect in a few hours. Treatment should be continued for several days after the pain and signs of inflammation have resolved to prevent relapse.

Oral colchicine, a traditional therapy, often produces a dramatic response if begun soon after the onset of symptoms. A dose of 1.2 mg can be followed with 0.6 mg 1 h later; joint pain tends to decrease after 12 to 24 h and sometimes ceases within 3 to 7 days. If colchicine is

tolerated, 0.6 to 1.2 mg once/day can be continued as the attack subsides. Drug interactions, especially with clarithromycin, may warrant reduction of dosage or use of other treatments.

Corticosteroids are sometimes used to treat acute attacks. Aspiration of affected joints, followed by instillation of corticosteroid ester crystal suspension, is very effective, particularly for monarticular symptoms; prednisolone tebutate 4 to 40 mg or prednisolone acetate 5 to 25 mg can be used, with dose depending on the size of the affected joint. Oral prednisone (about 0.5 mg/kg once/day), IM or IV corticosteroids, or single-dose ACTH 80 U IM is also very effective, particularly if multiple joints are involved. As with NSAID therapy, corticosteroids should be continued until after the attack fully resolves to prevent relapse.

In addition to NSAIDs or corticosteroids, supplementary analgesics, rest, ice application, and splinting of the inflamed joint may be helpful. Because lowering the serum urate level during an attack may prolong the attack or predispose to recurrence, drugs that lower the serum urate level should not be initiated until acute symptoms have been completely controlled. If corticosteroids, colchicine, and NSAIDs are contraindicated, an IL-1 antagonist, such as anakinra, can be used, although it is expensive.

Prevention of recurrent attacks:

The frequency of acute attacks is reduced by taking one to two 0.6-mg tablets of colchicine daily (depending on tolerance and severity). An extra two 0.6-mg tablets of colchicine taken at the first suggestion of an attack may abort flares. If the patient is taking prophylactic doses of colchicine and has had higher doses of colchicine to treat an acute attack within the past 2 wk, an NSAID should be used instead to try to abort the attack. A (reversible) neuropathy or myopathy can develop during chronic colchicine ingestion. This condition may occur in patients with renal insufficiency, in patients also receiving a statin or macrolide, or in patients with none of these risk factors. Attack frequency can also be decreased with daily low-dose NSAIDs.

Lowering the serum urate level:

Colchicine, NSAIDs, and corticosteroids do not retard the progressive joint damage caused by tophi. Such damage can be prevented and, if present, reversed with urate-lowering drugs. Tophaceous deposits are resorbed by lowering serum urate. Lowering serum urate may also decrease the frequency of acute arthritic attacks. This decrease is accomplished by

- Blocking urate production with allopurinol or febuxostat
- Increasing urate excretion with a uricosuric drug
- Using both types of drugs together in severe tophaceous gout

Hypouricemic therapy is indicated for patients with

- Tophaceous deposits
- Frequent or disabling attacks of gouty arthritis despite prophylactic colchicine, an NSAID, or both
- Urolithiasis
- Multiple comorbidities (eg, peptic ulcer disease, chronic kidney disease) that are relative contraindications to the drugs used to treat acute attacks (NSAIDs or corticosteroids)

Hyperuricemia is not usually treated in the absence of gout.

The goal of hypouricemic therapy is to lower the serum urate level. If tophi are not present, a reasonable target level is < 6 mg/dL (0.36 mmol/L), which is below the level of saturation (> 7.0 mg/dL [> 0.41 mmol/L] at normal core body temperature and pH). If tophi are present, the goal is to dissolve them, and this requires a lower target level. A reasonable target level is 5 mg/dL (0.30 mmol/L), and the lower the urate level, the faster tophi resolve. These target levels should be maintained indefinitely. Low levels are often difficult to maintain.

Drugs are effective in lowering serum urate; dietary restriction of purines is less effective, but high intake of high-purine food, alcohol (beer in particular), and nonalcoholic beer should be avoided. Carbohydrate restriction and weight loss can lower serum urate in patients with insulin resistance because high insulin levels suppress urate excretion. Intake of low-fat dairy products should be encouraged. Because acute attacks tend to develop during the first months of hypouricemic therapy, such therapy should be started in conjunction with once or twice

daily colchicine or NSAIDs and during a symptom-free period. Resolution of tophi may take many months even with maintenance of serum urate at low levels. Serum urate should be measured periodically, usually monthly while determining required drug dosage and then yearly to confirm the effectiveness of therapy.

Allopurinol, which inhibits urate synthesis, is the most commonly prescribed hypouricemic therapy. Uric acid stones or gravel may dissolve during allopurinol treatment. Treatment begins with 100 mg po once/day and can be increased up to 800 mg po once/day, or even higher, to achieve target serum urate levels. Some clinicians recommend decreasing the starting dose in patients with renal insufficiency to decrease the incidence of rare but severe systemic hypersensitivity reactions; however, no data confirm the effectiveness of this intervention. The final dose of allopurinol should be determined by the target serum urate level. The most commonly used daily dose is 300 mg but this dose is adequate for < 50% of patients with gout. Adverse effects include mild GI distress and skin rash, which can be a harbinger of Stevens-Johnson syndrome, life-threatening hepatitis, vasculitis, or leukopenia. Adverse effects are more common among patients with renal dysfunction. Some ethnic groups (eg, Koreans with renal disease, Thai, and Han Chinese) are at high risk of allopurinol reactions; HLA B*5801 is a marker for that risk in these ethnic groups.

Febuxostat is a far more costly but potent inhibitor of urate synthesis. It is especially useful in patients who do not tolerate allopurinol, have contraindications to allopurinol, or in whom allopurinol does not sufficiently decrease urate levels. It is begun at 40 mg po once/day and increased to 80 mg po once/day if urate does not decrease to < 6 mg/dL. Febuxostat is contraindicated in patients taking azathioprine or mercaptopurine because it can decrease metabolism of these drugs. Transaminase levels can become elevated and should be measured periodically.

Uricase can also be given but is not yet routinely used. Uricase is an enzyme that converts urate to allantoin, which is more soluble. IV uricase transiently lowers serum urate by a large amount. It decreases urate so much that crystal deposits are partially solubilized, leading to intra-articular release and acute flares in up to 70% of uricase treatment courses. Allergic infusion reactions (anaphylaxis in 6.5% of patients and other infusion reactions in 25 to 40% of patients) may occur with uricase treatment despite pretreatment with corticosteroids and/or antihistamines. Pegloticase (a pegylated form of recombinant uricase) is usually used and is very expensive. Pegloticase is contraindicated in patients with G6PD deficiency because it can cause hemolysis and methemoglobinemia. Failure of urate levels to decrease to < 6 mg/dL after pegloticase treatment predicts pegloticase antibodies and a high risk of future allergic reactions. To prevent other urate-lowering drugs from masking the ineffectiveness of pegloticase, other urate-lowering drugs should not be used with pegloticase.

Uricosuric therapy is useful in patients who underexcrete uric acid, have normal renal function, and have not had renal stones. It usually involves probenecid or sulfinpyrazone. Probenecid treatment begins with 250 mg po bid, with doses increased as needed, to a maximum of 1 g po tid. Sulfinpyrazone treatment begins with 50 to 100 mg po bid, with doses increased as needed, to a maximum of 100 mg po qid. Sulfinpyrazone is more potent than probenecid but is more toxic. Low doses of salicylates may worsen hyperuricemia but only trivially.

Other treatments:

Fluid intake ≥ 3 L/ day is desirable for all patients, especially those who chronically pass urate gravel or stones. Alkalinization of urine (with K citrate 20 to 40 mEq po bid or acetazolamide 500 mg po at bedtime) is also occasionally effective for patients with persistent uric acid urolithiasis despite hypouricemic therapy and adequate hydration. However, excessive urine alkalinization may cause deposition of Ca oxalate crystals. Extracorporeal shock wave lithotripsy may be needed to disintegrate renal stones. Large tophi in areas with healthy skin may be removed surgically; all others should slowly resolve under adequate hypouricemic therapy. Losartan has mild uricosuric effects.

Equipment: training room, ultrasound machine, X-ray machine.

Lesson duration: 2 hours

Plan

1. Organizational moment (greetings, checking the audience, the message of the topic, the purpose of the lesson, the motivation of applicants to study the topic).
2. Control of basic knowledge (initial survey with tests of the STEP 2 format – attached, check of workbooks on the topic):
2.1. Requirements for theoretical readiness of applicants to perform practical classes.
Knowledge requirements:

- Definition of gout
- Current views on the etiology and pathogenesis of gout
- Classification of gout
- Clinical presentation of gout
- Diagnostic of gout
- Differential diagnostic
- Complications of gout
- Treatment of gout
- Prognosis for patients with gout
- Primary and secondary prophylaxis of gout

List of didactic units:

- to collect in detail the anamnesis of the disease;
- to conduct a physical examination of the patient, to identify and assess changes in his condition;
- make a plan for additional examination, evaluate its results;
- formulate and substantiate a preliminary and clinical diagnosis of gout, taking into account the severity of disorders according to the classification, comprehensive assessment of patients;
- assessment of possible complications of gout;
- evaluation of the results of general clinical examination, laboratory analysis of blood, data of X-rays, CTs, MRIs, ultrasound, etc.

2.2. Questions (tests, tasks, clinical cases) to test basic knowledge on the topic of the lesson:

The tests with standard answers.

1. A 40-year-old male complains of exquisite pain and tenderness over the left ankle. There is no history of trauma. The patient is taking a mild diuretic for hypertension. On exam, the ankle is very swollen and tender. There are no other physical exam abnormalities. The next step in management is:

A. Begin colchicine and broad-spectrum antibiotics
B. Obtain uric acid level and perform arthrocentesis
C. Begin allopurinol if uric acid level is elevated
D. Obtain ankle x-ray to rule out fracture
E. Perform MRI for both ankle joints

2. A 72-year-old man presents to the emergency department with pain in his right big toe. The pain started this morning and is getting progressively worse, and he is unable to bear weight on that foot. This is his fifth presentation to the emergency department in the past 7 years for similar complaints. He says his doctor gave him a medication to prevent the attacks, but he does not remember the name and has not taken it in many months. He is febrile, has a pulse of 90/min, and has a blood pressure of 136/86 mm Hg. The first metatarsophalangeal joint of the right foot is swollen, warm, and erythematous. It is exquisitely tender to palpation and there is decreased movement. He also has several nontender nodules on the medial aspect of the big toes bilaterally, alongside the first

metacarpophalangeal joints bilaterally, and on his ears. Which of the following is the best agent for the acute management of this patient's condition?

A. Acetaminophen
B. Allopurinol
C. Indomethacin
D. Febuxostat
E. Probenecid

3. A 65-year-old man presents to the emergency department with severe pain (rated 10 of 10) in his right first toe. The pain started suddenly last night with no precipitating trauma. His toe is extremely tender to the touch, and is very warm and swollen. Your diagnosis?

A. Ankylosing spondylitis
B. Fibromyalgia
C. Gonococcal arthritis
D. Gout
E. Osteoarthritis

Clinical case with standards answers:

1. Patient M., age 55, a driver, complaining about swelling and pain in his right ankle and small joints of the right foot, red skin on them, restriction of movement in them.

Anamnesis revealed that suffers a sudden attack of pain in the joints of the right foot for about 8 years when the during the night appeared intense pain in the first finger of his right foot. At the same time it was discovered swelling, redness and increased skin temperature in the lesion. Self-acceptance analgesics led to a significant decrease in pain and restore function of the joints. Later it was found that recurrence of arthritis 1 st metatarsal-phalanx joint occurs after the holiday feasts or intensive physical work. Pain in the right ankle had joined in the last 6 months.

OBJECTIVE: hyperstenic, obese. In the cartilage of auricles palpable painless solid nodes value of 0,3 x 0,2 cm, whitish at the bend. Skin clean and sufficient moisture. Turgor pressure maintained. There have bone deformation in the 1 st and 2 nd metatarsal-phalanx joint of right foot with the formation of hallus valgus, combined with swelling, redness of the skin and increase the local temperature over the same joints. Symptom of lateral compression right foot positive. Slight limitation of movement 1 st and 2 nd fingers of the right foot. The right ankle is swollen, hot and painful on palpation. The volume of active and passive movements in it is limited due to pain. The internal organs without significant changes.

CBC: Hb - 158 g / l, Er. - 4,5 $x10^{12}$ / l, L. - 7,9$x10^{9}$ / l, ESR - 26 mm / h. Glucose - 4.66 mmol / l, PTI - 87%. Bilirubin - 13.5 mcmol / l, cholesterol - 5.8 mmol / l, creatinine - 65 mcmol / l, uric acid - 589 mcmol / l, CRP - 2, rheumatoid factor - 0, ASL-O - 125 units., sialic acid - 2.99 mmol / l, total protein - 77.5 g / l, protein fractions - albumin - 53%, globulins a1 - 3%, a2 - 9%, β- 14%, γ - 21%. Urinalysis: 1015, the reaction of weakly acidic, protein - 0,066 g / l, Er. - 0-2, L. - 2-4 in f / v.

Investigation of synovial fluid: the presence of needle-shaped crystals, located intracellularly and birefringent light in the polarizing microscope. Cytosis 10 000 - 60 000 cells per mm3 (predominantly neutrophils).

Aspiration of tophus content - presence of uric acid crystals.

Nechiporenko test: Er. - 1000$x10^{3}$ / l, L. - 4000$x10^{3}$ / l. Zimnitskiy test: daily urine output - 1200 ml, night output - 700 ml, sp. gravity - 1003-1015 units.

1. Primary clinical diagnosis.
2. Plan of investigation.
3. Treatment.

Answering standards

1. Gout, a mixed form, oligoarthritis 1^{st} and 2^{nd} right metatarsal-phalanx joints and right ankle, the activity of 1-2 degrees. Gout nephropathy. Secondary oligoosteoartrosis 1^{st} and 2^{nd} metatarsal-phalanx and ankle joints on the right.

2. CBC, urine test, uric acid, rheumatoid factor, ASL-O, sialic acid, protein fraction, the study of synovial fluid for the presence of crystals urine acid sodium by polarizing microscopy, aspiration of the contents tophi on crystals of uric acid. Ultrasound of the kidneys, urine Nechiporenko Zimnitskiy and, if necessary - renography and computed tomography of the kidneys, consulting urologist, ECG, x-rays of affected joints.
3. Relief of acute attacks of Gout: a) rest and immobilization of the affected joints b) diet with restriction of foods rich in purines and avoiding alcohol); c) high doses of NSAIDs short course d) in the absence of effect it is recommended intraarticular injection of glucocorticoids. Basic therapy in this case will consist of dieting and taking allopurinol for 4-6 months under the control of the level of uric acid in the blood.

III. Formation of professional skills, abilities (mastering the skills of curation, determining the treatment regimen):

1.1. Content of tasks:

Recommendations for tasks: (professional algorithms):

Work at the patient's bedside (according to the algorithm of communication between students and patients).

When examining patients, applicants must follow the following communication algorithms:

Collection of complaints and anamnesis in patients with internal diseases

1. Friendly facial expression, smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Collection of complaints and medical history of the patient.
5. Explanation of survey results.
6. Explanation of actions (hospitalization, conducting certain examinations) that are planned to be performed in the future.
7. End the conversation.

Physical methods of examination of patients with internal diseases

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Explain to the patient which examination will be performed and obtain his consent.
6. Warning about the possibility of unpleasant feelings during the examination.
7. Preparation for the examination (clean warm hands, trimmed nails, warm phonendoscope, if necessary - use a screen).
8. Conducting an examination (demonstration of clinical skills).
9. Explanation of survey results.
10. End the conversation.

Reporting the results of the examination to patients with internal diseases.

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the results of a particular examination.
5. Involve the patient in the interview (compare the results of this examination with previous results, find out if they understand your explanations).
6. End the conversation.

Planning and forecasting the results of conservative treatment:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the need for prescribed treatment.
5. Involvement of the patient (emphasis on the peculiarities of the drugs, duration of administration, possible side effects; find out whether the patient understands your explanations).
6. End the conversation.

Treatment prognosis message:

1. A friendly expression on the doctor's face, a smile.
2. Gentle tone of conversation.
3. Greetings and introductions, expression of interest, respect and care.
4. Correct and accessible to the patient's understanding explanation of the expected results of the prescribed treatment.
5. Involve the patient in the conversation (emphasis on the importance of continuous treatment, adherence to the prescribed treatment regimen, finding out whether your explanations are clear to the patient).
6. End the conversation.

Work 1.

1. Collection of complaints, anamnesis, examination of a patient with acute rheumatic fever.
2. Detection of clinical symptoms.
3. Grouping of symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data (clinical analysis of blood, urine, biochemical analysis of blood, chest X-ray or chest CT-scan, X-ray of joints or MRI or ultrasound of joints, ECG, echocardiography, etc.).
6. Carrying out of the differential diagnosis with other arthritis.
7. Formulation of the clinical diagnosis.
8. Determining the degree of disability.

Work 2.

Appointment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the cathedral library with thematic literature.

The student fills in the protocol of examination of the patient in writing. An example of the initial examination of the patient is attached.

Control materials for the final stage of the lesson:

Tasks for self-control with answers.

1. Patient 42 years old. Complaints: intense pain in big toe of his right foot that appeared sharply at night. On the eve he celebrated his birthday. On examination - the signs of inflammation of metacarpophalangeal joint of the big toe of right foot. ASLO 250 U, CRP (+++), urine acid 0,72 mmol/l. Primary diagnosis?

A. Rheumatoid arthritis

B. Gout arthritis
C. Reactive arthritis
D. Reumatic arthritis
E. Reyter's disease

2. Patient 43 years old, said about periodic pain in the joints (toes, ankles, knees, elbows), which occurs after eating meat, beans, alcohol. Over the past 3 weeks there was painless mobile tumor on extensor surfaces of elbows. Of what disease you might think?

A. Rheumatoid arthritis
B. Gout arthritis
C. Reactive arthritis
D. Reumatic arthritis
E. Osteoarthrosis

3. Patient 53 years old. Suffer from gout for about 8 years. Last 4 years noticed tophi on elbows. Disturbance of what type of metabolism underlies this disease?

A. Violation of purine metabolism
B. Violation of carbohydrate metabolism
C. Violation of protein metabolism
D. Violation of lipid metabolism
E. Violation of acid-base balance

4. Patient 63 years old, suffered from gout for 15 years. During hospitalization on X-rays of feet joints revealed large cysts near the proximal interphalangeal joints of the feet and minor erosion of the joint surfaces, periarticular soft tissue calcifications. What is the radiological stage of gout meet these changes?

A. I stage
B. II stage
C. III stage
D. Does not meet any one stage
E. These changes are not characteristic for gout

5. Patient 55 years, on the auricles are determined tight formation with a diameter up to 2 mm. Some days ago - acute pain in a 1-st tarsofalangeal joint of left foot, with hyperemia of the skin over it. Objectively: BP 150/100 mmHg. Laboratory tests: creatinine 100 μmol/l, uric acid 500 μmol/l. Which drug listed, you must assign?

A. Azatioprin
B. Indometacine
C. Hipothyazide
D. Sulfasalazine
E. **Allopurinol**

6. Male 49 years old, complaints about sharp pain in the tarsophalangeal joint of the big toe. On examination of the joint - edema, hyperemia. The X-ray - large (5-7 mm), pressed defects of epiphyses. What laboratory change is typical for this disease?

A. Rheumatoid factor
B. Eosinophilia
C. Hyperuricemia
D. Antinuclear antibody
E. Bacteriemia

7. A 47-year-old obese man complained of periodic attacks of acute arthritis in the different joint. Initial site - 1st left tarsophalangeal joint. Lab exam revealed increased serum rate of uric acid. What is the diagnosis?

A. Gout arthritis
B. Reiter's disease
C. Rheumatoid arthritis
D. Rheumatic arthritis

E. Osteoarthritis

List of recommended literature source:

Basic:

21. FitzGerald J.D., Dalbeth N., Mikuls T. et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis Care & Research, 2020; Vol. 72, No. 6: P.744–760.
22. Richette P, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017;76:29–42.
23. Rheumatology: Principles and Practice. Ed.by S. Princeton. HAYLE MEDICAL, 2019. 248 p.
24. ABC of Rheumatology, 5th edition. Ed. by A.Adebajo and L.Dunkley. Hoboken, NJ : John Wiley & Sons, Inc., 2018. 209 p.
25. Rheumatology Secrets, 4th edition. Ed.by S.G. West, J. Kolfenbach. Elsevier, 2020. 744 p.

Additional:

9. Kelley and Firestein's Textbook of Rheumatology. 10th ed. / G.S. Firestein, I.B.McInnes et al. – Elsevier Health Sciences, 2017. - 1794 p.
10. Therapeutic Guidelines Rheumatology. – Therapeutic Guidelines Limited, 2017. – 335 p.

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European male of 52 years old.

Complaints: of unbearable pain in the joints, mainly small joints of the hands and feet, wrist, ankle, aggravated by movement, touch, their swelling, increased skin temperature over them, impaired motor functions, general weakness, fatigue. Also worried about pain in the kidney area, increased blood pressure.

Medical history: Considers himself ill for 20 years, since the joints began to swell periodically. Previously, he was diagnosed with Gout, was treated, followed a diet. The condition worsened 2 weeks ago, when, after suffering psychoemotional stress (death of his son) and a period of dieting, the aforementioned complaints appeared. He turned to a private medical center for help, received treatment with NSAIDs and chondroprotectors without significant effect. He used prolonged glucocorticosteroids on his own without significant effect. He turned to the therapeutic department for help, - hospitalization, examination and treatment were recommended.

Life history: Material and living conditions are satisfactory. He denies tuberculosis, sexually transmitted diseases, viral hepatitis, malaria. Bad habits – smokes, recently drank alcohol. Lives in a family. Allergic history: there were no allergic reactions. Hereditary history is not burdened. He has not been in contact with infectious patients in the last 3 weeks.

Objective examination: General condition of the patient of moderate severity. Patient with increased nutrition. The skin and visible mucous membranes are pale. Peripheral lymph nodes are not enlarged. The thyroid gland is not enlarged. Percussion – above the lungs – pulmonary sound. Vesicular breathing, no wheezing. Breath rate - 18 in 1 min. Borders of relative cardiac dullness: upper – 3rd rib, right – right edge of the sternum, left – expanded to the left to the midclavicular line in the 5th intercostal space. Heart rhythmic activity, muted tones, accent of 2 tones on the aorta. BP 130/85 mm Hg, heart rate 72 in 1 min. Pulse 72 in 1 min, rhythmic. Tongue moist, thickly coated with white bloom. The abdomen is soft, painless on superficial palpation. The liver comes out from under the edge of the costal arch by 2 cm, its edge is painless on palpation. The spleen is not palpable. Pounding along the lumbar region is sharply painful. Body temperature 38.5C. The hands are swollen, hot to the touch, the ankle joints are swollen, hot to the touch, palpation of the joints is sharply painful.

Preliminary diagnosis:

Gout, gouty arthritis affecting the small joints of the hands, feet, wrist joints, ankle joints, exacerbation stage. Gouty nephropathy. Secondary chronic pyelonephritis in the acute stage,.

Hypertension, stage 2, stage II, risk 4.

Violation of carbohydrate tolerance.

Survey plan

- Complete blood count,
- Blood biochemistry, including rheumatic tests, glucose, glucose profile, glycated hemoglobin, kidney function tests, liver enzymes etc.
- Urine analysis,
- ECG,
- X-ray of joints, lungs,
- Ultrasound of the kidneys.

Treatment plan

- Ethoricoxib 40 mg i.m. OD
- Colchicine 1 mg BID orally
- Methylprednisolone 125 mg i.v. OD
- Levofloxacin 500 mg i.v. BID
- Paracetamol 1000 mg i.v. OD
- Losartan 100 mg OD orally

- Nifedipine 10 mg BID orally
- Bisoprolol 10 mg OD orally
- Omeprazole 40 mg BID orally

Appendix 2.

Tests of the initial level of knowledge of the KROK format

Topic 7. Gout

1. A 47-year-old obese man complained of periodic attacks of acute arthritis in the different joint. Initial site - 1st left tarsophalangeal joint. Lab exam revealed increased serum rate of uric acid. What is the diagnosis?
   A. Gout arthritis
   B. Reiter's disease
   C. Rheumatoid arthritis
   D. Rheumatic arthritis
   E. Osteoarthritis

2. A 72-year-old man presents to the emergency department with pain in his right big toe. The pain started this morning and is getting progressively worse, and he is unable to bear weight on that foot. This is his fifth presentation to the emergency department in the past 7 years for similar complaints. He says his doctor gave him a medication to prevent the attacks, but he does not remember the name and has not taken it in many months. He is febrile, has a pulse of 90/min, and has a blood pressure of 136/86 mm Hg. The first metatarsophalangeal joint of the right foot is swollen, warm, and erythematous. It is exquisitely tender to palpation and there is decreased movement. He also has several nontender nodules on the medial aspect of the big toes bilaterally, alongside the first metacarpophalangeal joints bilaterally, and on his ears. Which of the following is the best agent for the acute management of this patient's condition?
   A. Acetaminophen
   B. Allopurinol
   C. Indomethacin
   D. Febuxostat
   E. Probenecid

3. A 65-year-old man presents to the emergency department with severe pain (rated 10 of 10) in his right first toe. The pain started suddenly last night with no precipitating trauma. His toe is extremely tender to the touch, and is very warm and swollen. Your diagnosis?
   A. Ankylosing spondylitis
   B. Fibromyalgia
   C. Gonococcal arthritis
   D. Gout
   E. Osteoarthritis

4. Patient 42 years old. Complaints: intense pain in big toe of his right foot that appeared sharply at night. On the eve he celebrated his birthday. On examination - the signs of inflammation of metacarpophalangeal joint of the big toe of right foot. ASLO 250 U, CRP (+++), urine acid 0,72 mmol/l. Primary diagnosis?
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5. Patient 43 years old, said about periodic pain in the joints (toes, ankles, knees, elbows), which occurs after eating meat, beans, alcohol. Over the past 3 weeks there was painless mobile tumor on extensor surfaces of elbows. Of what disease you might think?
   A. Rheumatoid arthritis
   B. Gout arthritis
   C. Reactive arthritis
   D. Reumatic arthritis

E. Osteoarthrosis

6. Patient 53 years old. Suffer from gout for about 8 years. Last 4 years noticed tophi on elbows. Disturbance of what type of metabolism underlies this disease?

A. Violation of purine metabolism
B. Violation of carbohydrate metabolism
C. Violation of protein metabolism
D. Violation of lipid metabolism
E. Violation of acid-base balance

7. Patient 63 years old, suffered from gout for 15 years. During hospitalization on X-rays of feet joints revealed large cysts near the proximal interphalangeal joints of the feet and minor erosion of the joint surfaces, periarticular soft tissue calcifications. What is the radiological stage of gout meet these changes?

A. I stage
B. II stage
C. III stage
D. Does not meet any one stage
E. These changes are not characteristic for gout

8. Patient 55 years, on the auricles are determined tight formation with a diameter up to 2 mm. Some days ago - acute pain in a 1-st tarsofalangeal joint of left foot, with hyperemia of the skin over it. Objectively: BP 150/100 mmHg. Laboratory tests: creatinine 100 μmol/l, uric acid 500 μmol/l. Which drug listed, you must assign?

A. Azatioprin
B. Indometacine
C. Hipothyazide
D. Sulfasalazine
E. Allopurinol

9. Male 49 years old, complaints about sharp pain in the tarsophalangeal joint of the big toe. On examination of the joint - edema, hyperemia. The X-ray - large (5-7 mm), pressed defects of epiphyses. What laboratory change is typical for this disease?

A. Rheumatoid factor
B. Eosinophilia
C. Hyperuricemia
D. Antinuclear antibody
E. Bacteriemia

10. A 40-year-old male complains of exquisite pain and tenderness over the left ankle. There is no history of trauma. The patient is taking a mild diuretic for hypertension. On exam, the ankle is very swollen and tender. There are no other physical exam abnormalities. The next step in management is:

A. Begin colchicine and broad-spectrum antibiotics
B. Obtain uric acid level and perform arthrocentesis
C. Begin allopurinol if uric acid level is elevated
D. Obtain ankle x-ray to rule out fracture
E. Perform MRI for both ankle joints

Standard answers: 1-A, 2-C, 3-D, 4-B, 5-B, 6-A, 7-C, 8-E, 9-C, 10-B.

Practical lesson № 13-14
Topic 8: Glomerulonephritis. Renal Amyloidosis

Object: To teach applicants to master the method of examination of patients with nephrology diseases with the selection of the main syndromes. To study probable etiological factors, pathogenesis of Glomerulonephritis and Renal Amyloidosis, their main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis and efficiency of patients.

Basic concepts:

№	Term	Definition
1	Nephritic syndrome	clinical syndrome that presents as hematuria, elevated blood pressure, decreased urine output, and edema
2	Nephrotic syndrome	the combination of nephrotic-range proteinuria (more than 3.5 gr. per day), low serum albumin level, hyperlipidemia and edema.
3	Kidney biopsy	procedure to remove a small piece of kidney tissue that can be examined under a microscope for signs of damage or disease.
4	Hematuria	presence of blood or red blood cells in the urine.
5	Proteinuria	increased levels of protein in the urine.
6	Albuminuria	pathological condition wherein the protein albumin is abnormally present in the urine. It is a type of proteinuria.

Glomerulonephritis (GN) denotes glomerular injury and applies to a group of diseases that are generally, but not always, characterised by inflammatory changes in the glomerular capillaries and the glomerular basement membrane (GBM). The injury can involve a part or all of the glomeruli or the glomerular tuft. The inflammatory changes are mostly immune mediated. Diseases include membranous GN, minimal change disease, focal and segmental glomerulosclerosis, immunoglobulin A nephropathy, forms of rapidly progressive GN (vasculitis and anti-GBM disease), and systemic lupus erythematosus nephritis as the more common forms; and glomerular damage in other systemic diseases such as diabetes, amyloidosis, myeloma, and a variety of infections.

Aetiology
The disease can result from renal-limited glomerulopathy or from glomerulopathy-complicating systemic disease: for example, systemic lupus erythematosus (SLE) and vasculitis.

Glomerular injury may be caused by inflammation due to leukocyte infiltration, antibody deposition, and complement activation. Poorly understood non-inflammatory mechanisms may be responsible for some conditions as well.

It is commonly idiopathic, although increasingly it is possible to identify underlying causes.

Other causes include:

- Infections (group A beta-haemolytic Streptococcus, respiratory and gastrointestinal infections, hepatitis B and C, endocarditis, HIV, toxaemia, syphilis, schistosomiasis, malaria, and leprosy)
- Systemic inflammatory conditions such as vasculitides (SLE, rheumatoid arthritis, anti-glomerular basement membrane disease, granulomatosis polyangiitis, microscopic

polyangiitis, cryoglobulinaemia, Henoch-Schonlein purpura, scleroderma, and haemolytic uraemic syndrome)
- Drugs (penicillamine, gold sodium thiomalate, non-steroidal anti-inflammatory drugs, captopril, heroin, mitomycin C, cocaine, and anabolic steroids)
- Metabolic disorders (diabetes mellitus, hypertension, and thyroiditis)
- Malignancy (lung and colorectal cancer, melanoma, and Hodgkin's lymphoma)
- Hereditary disorders (Fabry's disease, Alport's syndrome, thin basement membrane disease, nail-patella syndrome, and hereditary complement protein disorders)
- Deposition diseases (amyloidosis and light chain deposition disease).

Classification

I. Primary/secondary diagnosis

Primary diagnosis: composed of 3 or 4 components in the following order:

1. Disease entity or pathogenesis/pathogenic type (when specific disease entity is not known)
2. Pattern of glomerular injury
3. Scores and/or class of the disease entity where appropriate
4. Additional disease-related features.

II. Nephrotic/nephritic classification

Nephrotic syndrome (nephrotic-range proteinuria, hypoalbuminaemia, hyperlipidaemia, and oedema)
- Deposition diseases
- Minimal change disease
- Focal and segmental glomerulosclerosis
- Membranous nephropathy
- Membranoproliferative GN.

Nephritic syndrome (haematuria, sub-nephrotic-range proteinuria, and hypertension)
- Immunoglobulin A nephropathy
- Postinfectious GN
- Rapidly progressive GN
    - Vasculitis
    - Anti-glomerular basement membrane (GBM) GN.

III. Nephritic and rapidly progressive GN (RPGN) classification

Nephritic and RPGN can be classified according to the immunofluorescence microscopy:
- Granular immune deposits (immune complex mediated)
- Linear immune deposits (anti-GBM)
- Pauci-immune (vasculitis).

RISK FACTORS

- Group A beta-haemolytic Streptococcus
- Respiratory infections (Associated with immunoglobulin A (IgA) nephropathy. May trigger recurrent episodes of gross haematuria, beginning 1 to 3 days post-infection)
- Gastrointestinal infections (Associated with IgA nephropathy. May trigger recurrent episodes of gross haematuria, beginning 1 to 3 days post-infection)
- Hepatitis B (Can result in the deposition of circulating antigen-antibody complexes in the mesangium and subendothelial space (causing membranoproliferative GN), in the subepithelial space (causing membranous nephropathy and nephrotic syndrome), or in the vessels (causing polyarteritis nodosa)
- Hepatitis C (The most common patterns of renal involvement are membranoproliferative GN (with cryoglobulinaemia) and, frequently, membranous nephropathy. The pathogenesis

appears to relate to deposition of immune complexes containing antibodies to the virus and viral RNA in the glomeruli)
- Infective endocarditis (membranoproliferative GN)
- HIV
- SLE (males, younger patients, and non-white Americans are at increased risk of developing nephritis earlier in the course of the disease)
- Systemic vasculitis (Such as classic polyarteritis nodosa, granulomatosis polyangiitis, microscopic polyarteritis, eosinophilic granulomatous polyangiitis (Churg-Strauss syndrome), and the hypersensitivity vasculitides (including Henoch-Schonlein purpura, mixed cryoglobulinaemia, and serum sickness)
- Hodgkin's lymphoma (Minimal change disease mostly occurs at the time of initial presentation, whereas renal amyloidosis is generally a late event)
- Lung cancer (associated with membranous nephropathy)
- Colorectal cancer (associated with membranous nephropathy)
- Non-Hodgkin's lymphoma (Minimal change disease or focal glomerulosclerosis)
- Leukemia (Minimal change disease, focal glomerulosclerosis, or membranoproliferative GN)
- Thymoma (Minimal change disease or focal glomerulosclerosis)
- Haemolytic uraemic syndrome (associated with membranoproliferative GN)
- Drugs (penicillamine, gold sodium thiomalate, non-steroidal anti-inflammatory drugs, captopril, mitomycin C, cocaine, and anabolic steroids)

CLINICAL MANIFESTATION

Milder forms of GN result in an asymptomatic illness. History, clinical examination, and laboratory testing may arouse clinical suspicion of the disease, but a biopsy is sometimes required for definitive diagnosis.

Early diagnosis with specialist referral, renal biopsy, and serological testing, and early initiation of appropriate therapy are essential to minimise the degree of irreversible renal injury.

Clinical assessment

Clinical features vary depending on the aetiology, and may include 1 or a combination of haematuria (macroscopic or more commonly microscopic), proteinuria, and oedema (characteristic of nephrotic syndrome). Hypertension may or may not be present; it is uncommon in nephrotic syndrome.

Patients may have features of the underlying disorder, for example:

- Joint pain, rash, and haemoptysis in vasculitis
- Fever and sore throat in streptococcal infections
- Jaundice in hepatitis B and C
- Weight loss in malignancies
- Stigmata of intravenous drug use

INVESTIGATION

1-st to order:

TEST	RESULT
urinalysis	
Dysmorphic red blood cells (RBCs), sub-nephrotic proteinuria, and active sediment points to the presence of GN.	haematuria, proteinuria, dysmorphic RBCs, leukocytes, and RBC casts
Comprehensive metabolic profile	
Elevated creatinine (indicates severe or advanced disease). Normal creatinine does not exclude significant renal pathology. Elevated liver enzymes may be seen if aetiology is related to hepatitis C virus or hepatitis B virus. Patients with nephrotic syndrome have hypoalbuminaemia.	normal or renal failure, elevated liver enzymes, hypoalbuminaemia
Glomerular filtration rate (GFR)	
Determined by mathematical equations such as the Modification of Diet in Renal Disease formula or CKD-EPI formula, the GFR gives an indication of the severity and stage of chronic kidney disease.	normal or reduced
Full blood count	
Anaemia is a feature of several systemic diseases that are associated with GN.	normocytic normochromic anaemia
Lipid profile	
May reveal hyperlipidaemia.	hyperlipidaemia or normal
Spot urine albumin:creatinine ratio (ASR)	
Quantifies proteinuria reasonably accurately and much more easily than a 24-hour urine collection, and should always be ordered as a follow-up to urinalysis showing proteinuria. If ACR is >220 mg/mmol, patients are classified as having nephrotic-range proteinuria and may have full nephrotic syndrome (hyperlipidaemia, hypoalbuminaemia, oedema, nephrotic-range proteinuria).	normal: urine ACR <220 mg/mmol; elevated: ACR >220 mg/mmol
Ultrasound of kidneys	
Thinning of the cortico-medullary junction and shrunken kidneys indicate a chronic process, thereby reducing the chances of treatment success. Helps differentiate from other causes of acute renal failure such as obstructive uropathy.	small kidneys or normal

Investigations to consider:

ESR and CRP	
Non-specific test; an elevated ESR or CRP indicates systemic inflammation, such as vasculitis.	elevated or normal

Complement levels	
Differentiates pauci-immune from immune complex GN.	low or normal C3 in immune complex diseases
Rheumatoid factor (RF)	
Positive result indicates rheumatoid arthritis or cryoglobulinaemia.	positive or normal
Anti-neutrophil cytoplasmic antibody (ANCA)	
Positive result indicates pauci-immune or anti-glomerular basement membrane disease. It is fairly specific but not very sensitive.	positive or normal
Anti-glomerular basement membrane (GBM) antibody	
Positive result indicates anti-GBM disease or Goodpasture's syndrome.	positive or normal
Antistreptolysine O antibody and antihyaluronidase	
high or rising titres indicate post-streptococcal GN.	high or rising titres, or normal
anti-DNase	
Positive result indicates post-streptococcal GN.	positive or normal
Anti-double-stranded DNA	
Positive result indicates systemic lupus erythematosus (SLE).	Positive result indicates systemic lupus erythematosus (SLE).
Antinuclear antibody	
High titres indicate SLE.	high titres, or normal
Cryoglobulins	
Positive result indicates cryoglobulinaemia.	Positive or normal
Hepatitis B and C serology	
HIV serology	
Electrophoresis	
Raised gamma-globulin associated with number of conditions including lymphoma, amyloidosis, and SLE. A monoclonal paraprotein indicates myeloma or AL amyloidosis.	monoclonal or polyclonal gammopathy or normal
Renal biopsy	
Should be urgently performed if glomerulonephritis is suspected. Core-needle biopsy remains the most sensitive and specific test for diagnosis. Light and electron microscopy will reveal pattern of cellular proliferation and number of glomeruli involved. Immunofluorescence and electron microscopy may show patterns of immune complex deposition.	characteristic findings on light, immunofluorescence, and electron microscopy
Antiphospholipase A2 receptors antibodies	
A positive result is highly specific and sensitive for idiopathic membranous GN.	Positive or normal
Chest CT or abdomen CT	
May be important to exclude malignancy in older patients.	normal or positive for malignancy

Simplified clinical severity classification

- Mild: asymptomatic isolated haematuria or proteinuria <2 g.
- Moderate to severe: symptomatic proteinuria, haematuria, and reduced GFR (nephrotic and nephritic syndromes and rapidly progressive GN).

TREATMENT

Acute

Mild disease:

1-st line - treatment of underlying cause + supportive measures

In general, patients who present with mild disease (isolated hematuria, minimal or no proteinuria, and a normal glomerular filtration rate [GFR]) do not need specific therapies other than treating the systemic cause (e.g., antibiotics, antivirals, withdrawal of the causative drug). Dietary intake of salt and water may need to be restricted.

Close monitoring is needed to check for progressive renal failure.

Adjunct: antibiotic therapy for SOME patients in selected patient group (amoxicillin/clavulanate 875 mg orally twice daily for 10 days, or cefalexin 500 mg orally twice daily for 10 days, or cefuroxime 250 mg orally twice daily for 10 days, or azithromycin 500 mg orally twice daily for 5 days)

Moderate-Severe disease:

1-st line - ACE-inhibitors and angiotensin- II receptors antagonists (ramipril 5 mg once daily, or lisinopril 10 mg once daily, or losartan 50-100 mg once daily)

Patients who present with haematuria, proteinuria, and reduced glomerular filtration rate are considered to have moderate to severe disease. ACE inhibitors or angiotensin-II receptor antagonists may be used to decrease proteinuria. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee has advised that combining drugs that act on the renin-angiotensin system should only be considered if absolutely necessary, and should be carried out under strict specialist supervision with close monitoring.

Adjunct: antibiotic for SOME patients in selected patient group (amoxicillin/clavulanate 875 mg orally twice daily for 10 days, or cefalexin 500 mg orally twice daily for 10 days, or cefuroxime 250 mg orally twice daily for 10 days, or azithromycin 500 mg orally twice daily for 5 days)

Adjunct: furosemide 40-120 mg/day orally. Hypertension, which may develop as a result of volume expansion and salt retention, will hasten renal damage and have cardiovascular complications, and requires aggressive management. Patients who remain hypertensive despite therapy with ACE inhibitors or angiotensin-II receptor antagonists may have added diuretic therapy.

With NEPROTIC SYNDROME

Plus:

prednisolone: 1 mg/kg/day orally, taper dose gradually once remission is induced

AND

cyclophosphamide: dose regimens vary; consult specialist for guidance on dose

or

azathioprine: 1-2 mg/kg/day orally

or

mycophenolate mofetil: 1 to 1.5 g orally twice daily

or

rituximab: dose regimens vary; consult specialist for guidance on dose

Patients who have nephrotic syndrome, including those who relapse after apparent remission, or those with moderate disease almost always need oral corticosteroids and, depending on the underlying cause, additional immunosuppressants from the outset. Treatment is critically dependent on the precise cause of the nephrotic syndrome.
Severe disease presenting as nephrotic syndrome (e.g., minimal change disease, focal and segmental glomerulosclerosis, and mesangioproliferative GN) is usually treated with a corticosteroid plus other immunosuppressants. A review of the literature suggests that a shorter course of oral corticosteroids (2 or 3 months) may be just as beneficial as a prolonged duration of treatment in children with nephrotic syndrome.
Rituximab, an anti-CD20 antibody that depletes B lymphocytes, is being increasingly used in many forms of GN, especially in patients with systemic lupus erythematosus (SLE) and vasculitis. All patients should be referred to a specialist for advice on immunosuppressant therapy.
Patients on high-dose corticosteroids require medications for prophylaxis of complications (e.g., omeprazole or lansoprazole, calcium, and vitamin D).

ONGOIND DESEASE (persistant hematuria, proteinuria and reduced GFR)
1-st line - ACE-inhibitors and angiotensin- II receptors antagonists
Plus - maintenance immunosuppression for several years depending on the underlying cause of the GN, with either low-dose prednisolone or drugs such as azathioprine or mycophenolate. The precise details vary with each disease, are individualised, and require specialist management.
Adjunct – furosemide (in Some patients groups)

MONITORING
The major parameters that are serially monitored are urine sediment, protein excretion (usually estimated from the urine protein-to-creatinine ratio), and the serum creatinine concentration. These should be obtained at 2- to 4-week intervals during the initial therapy and then at 1- to 2-month intervals once drug therapy is stabilised and/or is being tapered. Disease activity for individual aetiologies can be monitored by their specific antibody titres every 1 to 2 weeks during the initial therapy and then at 1- to 2-month intervals, or whenever there are signs suggestive of recurrence.

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

Complications of Nephrotic Syndrome

Complication	**Contributing Factors**
Edema (including ascites and pleural effusions)	Generalized capillary leak Possibly renal Na retention
Infection (especially cellulitis and, in 2 to 6%, spontaneous bacterial peritonitis)	Unknown Possibly loss of opsonins and immunoglobulins
Anemia	Loss of erythropoietin and transferrin
Changes in thyroid function test results (among patients previously hypothyroid, increased dose requirement for thyroid replacement hormone)	Loss of thyroid-binding globulin
Hypercoagulability and thromboembolism (especially renal vein thrombosis and pulmonary embolism, which occur in up to 5% of children and 40% of adults)	Loss of antithrombin III Increased hepatic synthesis of clotting factors Platelet abnormalities Hyperviscosity caused by hypovolemia

Protein undernutrition in children (sometimes with brittle hair and nails, alopecia, and stunted growth)	Loss of proteins Sometimes decreased oral intake secondary to mesenteric edema
Hyperlipidemia	Increased hepatic lipoprotein synthesis
Coronary artery disease in adults	Hyperlipidemia with atherosclerosis Hypertension Hypercoagulability
Hypertension in adults	Renal Na retention
Bone disorder	Corticosteroid use
Chronic kidney disease	Unknown Possibly hypovolemia, interstitial edema, and use of NSAIDs
Proximal tubular dysfunction (acquired Fanconi syndrome), with glucosuria, aminoaciduria, K depletion, phosphaturia, renal tubular acidosis, bicarbonaturia, hypercitraturia, and uricosuria	Toxic effects on proximal tubular cells secondary to large amounts of protein that they reabsorb

Symptoms and Signs

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

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

PROGNOSIS

Patients with post-streptococcal GN and immunoglobulin A (IgA) nephropathy have a low incidence of developing chronic kidney disease. Most patients, particularly children, eventually have complete clinical recovery from the initial episode. However, patients with IgA nephropathy and proteinuria are increasingly recognised to develop progressive CKD after 15 years.

For other glomerular diseases, the long-term prognosis tends to be better in patients who present with asymptomatic haematuria and proteinuria and who have focal, rather than diffuse, glomerular involvement on renal biopsy. Principal determinants of a relatively poor renal outcome include more severe renal dysfunction at presentation, more severe proteinuria, lack of response to initial treatment, and an enhanced amount of fibrotic changes, such as interstitial fibrosis and glomerulosclerosis on initial renal biopsy.

End-stage renal disease eventually occurs in up to 50% to 60% of untreated patients with membranoproliferative disease within 10 to 15 years,and in approximately 20% to 25% of patients with granulomatosis polyangiitis.

Amyloidosis

The amyloidoses are a group of disorders in which soluble proteins aggregate and deposit extracellularly in tissues as insoluble fibrils, causing progressive organ dysfunction. The kidney is one of the most frequent sites of amyloid deposition in AL, AA, and several of the hereditary amyloidoses.

Etiology

In **systemic amyloidosis,** circulating amyloidogenic proteins form deposits in a variety of organs. Major systemic types include

- AL (primary amyloidosis): Caused by acquired overexpression of clonal immunoglobulin light chains

- AF (familial amyloidosis): Caused by inheritance of a mutant gene encoding a protein prone to misfolding, most commonly transthyretin (TTR)
- SSA (senile systemic amyloidosis): Caused by misfolding and aggregation of wild-type TTR (thus also termed ATTRwt)
- AA (secondary amyloidosis): Caused by aggregation of an acute phase reactant, serum amyloid A

Amyloidosis caused by aggregation of β_2-microglobulin ($A\beta_2$) can occur in patients on long-term hemodialysis, but the incidence has declined with use of modern high-flow dialysis membranes.
Localized forms of amyloidosis appear to be caused by local production and deposition of an amyloidogenic protein (including immunoglobulin light chains) within the affected organ rather than by deposition of circulating proteins. Frequently involved sites include the CNS (eg, in Alzheimer disease), skin, upper or lower airways, bladder, and other sites.

AL amyloidosis
AL is caused by overproduction of an amyloidogenic immunoglobulin light chain in patients with a monoclonal plasma cell or other B cell lymphoproliferative disorder. Light chains can also form nonfibrillar tissue deposits (ie, light chain deposition disease). Rarely, immunoglobulin heavy chains form amyloid fibrils (AH). Common sites for amyloid deposition include the skin, nerves, heart, GI tract (including tongue), kidneys, liver, spleen, and blood vessels. Usually, a low-grade plasmacytosis is present in the bone marrow, which is similar to that in multiple myeloma, although most patients do not have true multiple myeloma (with lytic bone lesions, hypercalcemia, renal tubular casts, and anemia). However, about 10 to 20% of patients with multiple myeloma develop AL amyloidosis.

AA amyloidosis
This form can occur secondary to several infectious, inflammatory, and malignant conditions and is caused by aggregation of isoforms of the acute-phase reactant serum amyloid A. Common causative infections include TB, bronchiectasis, osteomyelitis, and leprosy. Inflammatory conditions include RA, juvenile idiopathic arthritis (formerly juvenile RA), Crohn disease, inherited periodic fever syndromes such as familial Mediterranean fever, and Castleman disease. Inflammatory cytokines (eg, IL-1, tumor necrosis factor, IL-6) that are produced in these disorders or ectopically by tumor cells cause increased hepatic synthesis of serum amyloid A.
AA shows a predilection for the spleen, liver, kidneys, adrenal glands, and lymph nodes. Involvement of the heart and peripheral or autonomic nerves is rare.

AF amyloidosis
AF is caused by inheritance of a gene encoding a mutated aggregation-prone serum protein, usually a protein abundantly produced by the liver. Serum proteins that can cause AF include transthyretin (TTR), apolipoprotein A-1, lysozyme, fibrinogen, gelsolin, and cystatin C. A recently identified form that is speculated to be familial is caused by the serum protein leukocyte chemotactic factor 2 (LECT2); however, a specific inherited gene mutation for this latter type has not been clearly demonstrated.
Amyloidosis caused by TTR (ATTR) is the most common type of AF. More than 100 mutations of the TTR gene have been associated with amyloidosis. The most prevalent mutation, V30M, is common in Portugal, Sweden, and Japan, and a V122I mutation is present in about 4% of American blacks. Disease penetrance and age of onset are highly variable but are consistent within families and ethnic groups. ATTR causes peripheral sensory and autonomic neuropathy and cardiomyopathy. Carpal tunnel syndrome is common. Vitreous deposits or cerebrovascular amyloid angiopathy may also develop due to production of mutant TTR by the retinal epithelium or choroid plexus, respectively.

SSA amyloidosis

SSA is caused by aggregation and deposition of wild-type TTR, mainly in the heart. SSA is increasingly recognized as a cause of infiltrative cardiomyopathy in older men. The genetic and epigenetic factors leading to SSA are unknown.

Because SSA and AL amyloidosis both can cause cardiomyopathy, and because monoclonal gammopathies not associated with amyloidosis may be present in patients in this age group, it is essential to accurately type the amyloid so that patients with SSA are not inappropriately treated with chemotherapy (which is used for AL).

Localized amyloidosis

Localized amyloidosis outside the brain is most frequently caused by deposits of clonal immunoglobulin light chains and within the brain by Aβ protein. Localized amyloid deposits typically involve the airways and lung tissue, bladder and ureters, skin, breasts, and eyes. Rarely, other locally produced proteins cause amyloidosis, such as keratin isoforms that can form deposits locally in the skin.

Aβ protein deposits in the brain contribute to Alzheimer disease or cerebrovascular amyloid angiopathy. Other proteins produced in the CNS can misfold, aggregate, and damage neurons, leading to neurodegenerative diseases (eg, Parkinson disease, Huntington disease). Clonal immunoglobulin light chains produced by mucosal-associated lymphoid tissue in the GI tract, airways, and bladder can lead to localized AL in those organs.

Symptoms and Signs

Symptoms and signs of systemic amyloidosis are nonspecific, often resulting in delays in diagnosis. Suspicion of amyloidosis should be increased in patients with a progressive multisystem disease process.

Renal amyloid deposits typically occur in the glomerular membrane leading to proteinuria, but in about 15% of cases the tubules are affected, causing azotemia with minimal proteinuria. These processes can progress to nephrotic syndrome with marked hypoalbuminemia, edema, and anasarca or to end-stage renal disease.

Hepatic involvement causes painless hepatomegaly, which may be massive. Liver function tests typically suggest intrahepatic cholestasis with elevation of alkaline phosphatase and later bilirubin, although jaundice is rare. Occasionally, portal hypertension develops, with resulting esophageal varices and ascites.

Airway involvement leads to dyspnea, wheezing, hemoptysis, or airway obstruction.

Infiltration of the myocardium causes a restrictive cardiomyopathy, eventually leading to diastolic dysfunction and heart failure; heart block or arrhythmia may occur. Hypotension is common.

Peripheral neuropathy with paresthesias of the toes and fingers is a common presenting manifestation in AL and ATTR amyloidoses. Autonomic neuropathy may cause orthostatic hypotension, erectile dysfunction, sweating abnormalities, and GI motility disturbances.

Cerebrovascular amyloid angiopathy most often causes spontaneous lobar hemorrhage but some patients have brief, transient neurologic symptoms.

GI amyloid may cause motility abnormalities of the esophagus and small and large intestines. Gastric atony, malabsorption, bleeding, or pseudo-obstruction may also occur. Macroglossia is common in AL amyloidosis.

A firm, symmetric, nontender goiter resembling that found in Hashimoto thyroiditis may result from amyloidosis of the thyroid gland; other endocrinopathies can also occur. Lung involvement (mostly in AL amyloidosis) can be characterized by focal pulmonary nodules, tracheobronchial lesions, or diffuse alveolar deposits. In several hereditary amyloidoses, amyloid vitreous opacities and bilateral scalloped pupillary margins develop.

Diagnosis

- Biopsy
- Amyloid typing

- Testing for organ involvement

Diagnosis of amyloidosis is made by demonstration of fibrillar deposits in an involved organ. Aspiration of subcutaneous abdominal fat is positive in about 80% of patients with AL or ATTR, but only about 50% of patients with SSA. If the fat biopsy result is negative, a clinically involved organ should be biopsied. Tissue sections are stained with Congo red dye and examined with a polarizing microscope for characteristic birefringence. Nonbranching 10-nm fibrils can also be recognized by electron microscopy on biopsy specimens from heart or kidney.

Amyloid typing

After amyloidosis has been confirmed by biopsy, the type is determined using a variety of techniques. For some types of amyloidosis, immunohistochemistry or immunofluorescence may be diagnostic, but false-positive typing results occur. Other useful techniques include gene sequencing for AF, and biochemical identification by mass spectrometry.

If AL is suspected, patients should be evaluated for an underlying plasma cell disorder using quantitative measurement of serum free immunoglobulin light chains, qualitative detection of serum or urine monoclonal light chains using immunofixation electrophoresis (serum protein electrophoresis and urine protein electrophoresis are insensitive in patients with AL), and a bone marrow biopsy with flow cytometry or immunohistochemistry to establish plasma cell clonality. Patients with > 10% clonal plasma cells should be tested to see if they meet criteria for multiple myeloma, including screening for lytic bone lesions, anemia, renal insufficiency, and hypercalcemia.

Organ involvement

Patients are screened for organ involvement beginning with noninvasive testing of kidney, liver, GI, nervous system, and cardiac function, particularly when symptoms suggest organ involvement. Patients should have urinalysis and measurement of serum BUN and creatinine to screen for renal involvement, liver function tests to screen for hepatic involvement, and ECG and measurement of brain (B-type) natriuretic peptide (BNP) or N-terminal-pro-BNP (NT-proBNP) and troponin to screen for cardiac involvement. Cardiac involvement can be suggested by low voltage on ECG (caused by a thickened ventricle), and/or dysrhythmias. If cardiac involvement is suspected because of symptoms, ECG, or cardiac biomarkers, echocardiography is done to measure diastolic relaxation and systolic function and to screen for biventricular hypertrophy. In ambiguous cases, cardiac MRI can be done to detect delayed subendocardial gadolinium enhancement, a characteristic finding. Lung involvement can be detected by chest x-ray, CT, and/or pulmonary function testing.

Prognosis

Prognosis depends on the type of amyloidosis and the organ system involved, but with appropriate disease-specific and supportive care, many patients have an excellent life expectancy.

AL complicated by severe cardiomyopathy still has the poorest prognosis, with median survival of < 1 yr. Untreated ATTR amyloidosis usually progresses to end-stage cardiac or neurologic disease within 10 to 15 yr. SSA typically has the slowest progression of any systemic amyloidosis involving the heart, but some patients do progress to symptomatic heart failure and death within a few years of diagnosis.

Prognosis in AA amyloidosis depends largely upon the effectiveness of treatment of the underlying infectious, inflammatory, or malignant disorder

Treatment

- Supportive care
- Type-specific treatment

Currently, there are specific treatments for most forms of amyloidosis, although some therapies are investigational. For all forms of systemic amyloidosis, supportive care measures can help relieve symptoms and improve quality of life.

Supportive care

Supportive care measures are directed at the affected organ system:

- **Renal** : Patients with nephrotic syndrome and edema should be treated with salt and fluid restriction, and loop diuretics; because of the ongoing protein loss, protein intake should not be restricted. Kidney transplantation is an option when the underlying disease process is controlled, and can provide long-term survival comparable to that in other renal diseases.
- **Cardiac:** Patients with cardiomyopathy should be treated with salt and fluid restriction and loop diuretics. Other drugs for heart failure, including digoxin, ACE inhibitors, Ca channel blockers, and β-blockers are poorly tolerated and contraindicated. Heart transplantation has been successful in carefully selected patients with AL amyloidosis and severe cardiac involvement. To prevent recurrence in the transplanted heart, patients must be given aggressive antiplasma cell therapy (usually IV melphalan) followed by autologous stem cell transplantation.
- **GI:** Patients with diarrhea may benefit from loperamide. Those with early satiety and gastric retention may benefit from metoclopramide.
- **Nerves** : In patients with peripheral neuropathy, gabapentin or pregabalin may relieve pain.

Orthostatic hypotension often improves with high doses of midodrine; this drug can cause urinary retention in older males, but supine hypertension is rarely a problem in this population. Support stockings can also help, and fludrocortisone can be used in patients without peripheral edema, anasarca, or heart failure.

Type-specific treatment

For **AL amyloidosis,** prompt initiation of antiplasma cell therapy is essential to preserve organ function and prolong life. Most drugs used for multiple myeloma (IgM Heavy Chain Disease) have been used in AL amyloidosis; choice of drug, dose, and schedule often must be modified when organ function is impaired. Chemotherapy using an alkylating agent (eg, melphalan, cyclophosphamide) combined with corticosteroids was the first regimen to show any benefit. High-dose IV melphalan, combined with autologous stem cell transplantation can be highly effective in selected patients. Proteasome inhibitors (eg, bortezomib) and immunomodulators (eg, lenalidomide) also can be effective. Combination and sequential regimens are being investigated. Localized AL can be treated with low-dose external beam radiation therapy because plasma cells are highly radiosensitive.

For **ATTR amyloidosis,** liver transplantation—which removes the site of synthesis of the mutant protein—can be effective in certain TTR mutations with early neuropathy and no heart involvement. Recently, certain drugs have been shown to stabilize TTR in the plasma, preventing misfolding and fibril formation and inhibiting neurologic disease progression while preserving quality of life. These TTR stabilizers include diflunisal, which is widely available, and tafamidis, which is available in Europe and Japan. TTR gene silencing using anti-sense RNA or RNA interference to block translation of mRNA into protein effectively reduces serum levels of TTR and is in clinical trials. These approaches should also be effective in SSA but have not been tested; liver transplantation is not effective for SSA patients because the amyloidogenic protein is wild-type TTR.

For **AA amyloidosis** caused by familial Mediterranean fever, colchicine 0.6 mg po once/day or bid is effective.Colchicine is not effective in other disorders predisposing to AA amyloidosis. For other AA types, treatment is directed at the underlying infection, inflammatory disease, or malignancy. Eprodisate, a sulfonated molecule that alters the stability of AA amyloid deposits, is a promising drug now under study.

Current treatment for AL-amyloidosis

Current regimes have been modified from multiple myeloma protocols, and treatment choice depends upon the type and severity of organ involvement—for example, cardiac involvement, peripheral neuropathy, or significant hypotension may preclude particular agents. These drugs are commonly combined with dexamethasone and are often used in conjunction with a myelosuppressive agent, such as cyclophosphamide.

Melphalan and dexamethasone have been used to reduce the production of aberrant light chains, and although 33% of 'intermediate-risk' patients achieved complete response (CR) with high-dose dexamethasone and a median survival of 5.1 years, CRs were halved in patients with significant cardiac AL (who could only tolerate low-dose dexamethasone), 26% of whom died during the period of treatment.

The potential advantage of *autologous stem cell transplantation (ASCT)* in delivering a longer remission-free period and a relatively quick CR) means that patients should be considered for this procedure from the onset. The depth of hematological response is associated with the degree of organ response, emphasizing the importance of trying to achieve CR either through chemotherapy alone or with ASCT.

Proteasome inhibitors

Bortezomib induces a rapid decrease in serum-free light-chain concentration in patients with myeloma. Purified plasma cells from amyloid patients are twice as vulnerable to bortezomib inhibition as those from myeloma patients. This is thought to be because amyloidogenic light chains have a greater propensity to misfold, thus overloading the proteasome. Its efficacy in achieving both a high hematological and organ response rate has led to it being adopted as a front-line therapy in AL amyloidosis

Equipment: class room, 6-channel ECG machine CARDIOLINE 100 L and Cardioline 200 + II S, ultrasound system

Mylab Six CristaLine with 3 detectors.

Lesson time: 4 hours

Plan

I. Organization moments (Greeting, head count, theme announce, aim of lesson, motivating applicants to study the topic).

II. Control of basic knowledges (The task source for self-knowledge skills tests from «KROK2» - additional materials, cheking workbooks)

II.1 Requirements for theoretical readiness of applicants to perform practical classes.

Requirements to knowledges:

- Definition of glomerulonephritis and renal amyloidosis
- Modern aspects of etiology and pathophysiology of glomerulonephritis and renal amyloidosis
- Classification of glomerulonephritis and renal amyloidosis
- Clinical manifestation of glomerulonephritis and renal amyloidosis
- Laboratory and instrumental investigation of glomerulonephritis and renal amyloidosis
- Carry out differential diagnosis of glomerulonephritis and renal amyloidosis
- Complications of glomerulonephritis and renal amyloidosis
- Treatment, rehabilitation of patients with glomerulonephritis and renal amyloidosis
- Prognosis and disability of patients with glomerulonephritis and renal amyloidosis

list of didactic units

- To get a detailed anamnesis
- To do physical examination of patient, to diagnose and to estimate changes in condition
- To make a plan of additional investigation and estimate it
- Justify and make a preliminary and clinical diagnoses of pyelonephritis and tubulointerstitial nephritis.
- Basic principles of treatment pyelonephritis and tubulointerstitial nephritis.
- Estimation of exacerbation of chronic pyelonephritis and tubulointerstitial nephritis and its treatment
- Estimation of clinical examination, CBC, blood tests, urinalysis, Nechiporenko`s test, Zimnitsky`s test, kidney ultrasound.

II.2 Questions (MSQ, clinical cases) for basic knowledge examination of topic

1. Chronic glomerulonephritis was diagnosed in a 34-year-old patient 3 years ago. Edema has developed in the last 6 months. What caused it?

A Disorder of concentrative kidneys function
B Hyperproduction of vasopressin
C Proteinuria +
D Hyperosmolarity of plasma
E Hyperaldosteronism

2. Two weeks after lacunar tonsillitis a 20-year-old man started complaining about general weakness, edema of lower eyelid. After examination the patient was diagnosed with acute glomerulonephritis. What are the most likely pathological changes in the urine?

A Proteinuria +
B Cylindruria
C Presence of fresh erythrocytes
D Pyuria
E Natriuria

3. A 30 year old woman has face edema. Examination revealed proteinuria (5,87 g/l), hypoproteinemia, dysproteinemia, hyperlipidemia. What condition is the set of these symptoms typical for?

A Nephritic syndrome
B Nephrotic syndrome +
C Chronic pyelonephritis
D Acute renal failure
E Chronic renal failure

4. For a patient A., 38 years, with 3 year of lupus disease found out the diffuse damage of kidney, which is accompanied massive edemas, expressed proteinuria, hyperlipidemia, dysproteinemia. What is the most reliable mechanism of proteinuria development in this clinical situation?

A. Nephrons inflammatory damage
B. Tubule ischemic damage
C. Increase the level of blood proteins
D. Nephron autoimmune damage +
E. Impression of urine ways

5. A patient, 19 years, in 2 weeks after tonsillitis appealed to the doctor with complaints about oliguria, discoloration of urine (“meat slops”). AP - 190/100 mm Hg. What the diagnosis is more likely?

A. Acute pyelonephritis
B. Acute glomerulonephritis +
C. Chronic glomerulonephritis
D. Chronic pyelonephritis

E. Chronic tubulointerstitial nephritis

III. Proffesional skills formation (skills of patient`s management, treatment)

Professional algorithms: work with a patient (according to patients-applicants conversation algorithm).

During examination students must use next algorithm:

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Collecting data on patient complains, medical history, life history
5. Interpretation of clinical, laboratory and instrumental studies
6. Explanation for patient of next acting (hospitalization, workup)
7. End of conversation

Physical examination of patient with internal diseases

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Explanation of investigations are needed, taking agreement
5. Telling about possible negative feelings during investigation
6. Preparing to examination (clean warm hands, accurate nails, warm phonendoscope, screen if needed)
7. Examination (demonstration of clinical skills)
8. Interpretation of clinical, laboratory and instrumental studies
9. End of conversation

Telling to patient with internal diseases investigation results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of investigation results
5. Conversation with patient (comparing new and previous examination results, check if explanation is clear)
6. End of conversation

Planning and prognosing treatment results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of treatment
5. Conversation with patient (explanation of features taking pills, duration of taking drugs, possible side effects)
6. Check if explanation is clear
7. End of conversation

Telling treatment prognosis

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of expected treatment results
5. Conversation with patient (explanation of importance of life-long treatment, taking medications according to list, check if explanation is clear)
6. End of conversation

Task 1

1. Collecting complains, anamnesis, examination of patients with glomerulonephritis and renal amyloidosis
2. Identify clinical and instrumental symptoms
3. Make a syndrome based on symptoms and lab. tests
4. Identify the leading clinical syndrome
5. Assign laboratory and instrumental examination (CBC, urine analysis, blood tests, Nechiporenko`s test, Zimnitsky`s test, kidney ultrasound)
6. Carry out differential diagnosis with glomerulonephritis and renal amyloidosis
7. Make a clinical diagnosis
8. Determine a degree of disability

Task 2

Prescribing different variants of treatment according to guidelines

Task 3

Work in Internet, work with thematic literature in department library room.

Student must fill patient examination protocol (example is added).

Control materials for final part of the lesson:

The cases for self-control with standard answers.

1. Patient 48 years, nephrotic syndrome was diagnosed. Complaints of general weakness, edema. During examination BP 90/60 mmHg, petechial paraorbital elements, macroglossia. Laboratory tests: a general analysis of urine protein 6.5 g / l, RBC 5-9 in f/v, WBC 3-4 in f/v., gravity 1023; biochemical tests: protein 45 g/l, creatinine 95 mcmol/l, urea 7,5 mmol/l, cholesterol 5,1 mmol/l. What the diagnosis is more likely?
A. Pyelonephritis
B. Glomerulonephritis
C. Amyloidosis
D. Renal failure
E. Chronic tubulointerstitial nephritis
2. Patient 48 years, nephrotic syndrome was diagnosed. Complaints of general weakness, edema. During examination BP 90/60 mmHg, petechial paraorbital elements. Laboratory tests: a general analysis of urine protein 8.5 g / l, RBC 15-20 in f/v, WBC 3-4 in f/v., gravity 1023; biochemical tests: protein 45 g/l, creatinine 95 mcmol/l, urea 7,5 mmol/l, cholesterol 8,1 mmol/l. . What is the best method of diagnosis to determine the future treatment strategy?
A. US of kidneys
B. Excretory urography
C. Dinamic renoscintigraphy
D. Renal biopsy
E. Zimnitskiy test
3. A 68-year-old female patient complains about temperature rise up to 38,3^{o}C,
haematuria. ESR- 55 mm/h. Antibacterial therapy turned out to be ineffective. What diagnosis might be suspected?
A. Renal cancer
B. Polycystic renal disease
C. Renal amyloidosis
D. Urolithiasis

E. Chronic glomerulonephritis

4. A 54-year-old patient has an over 20-year history of femoral osteomyelitis. Over the last month she has developed progressing edema of the lower extremities. Urine test reveals: proteinuria 6,6 g/l; in blood: hypoalbuminemia, increase in alpha_2- and gamma-globulin rate, ESR - 50 mm/h. What is the most likely diagnosis?

A. Myelomatosis

B . Acute glomerulonephritis

C. Secondary renal amyloidosis

D. Chronic glomerulonephritis

E. Systemic lupus erythematosus

5. A 58 y.o. patient complains of weakness, leg edema, dyspnea, anorexia. He has been suffering from chronic bronchitis for many years. During the last 5 years he has been noting intensified discharge of sputum that is often purulent. Objectively: HR- 80/min, BP- 120/80 mmHg. Disseminated edema, skin is dry and pale, low turgor. In urine: intense proteinuria, cylindruria. Specify the most probable pathological process in kidneys:

A. Acute glomerulonephritis

B. Chronic glomerulonephritis

C. Chronic pyelonephritis

D. Interstitial nephritis

E. Renal amyloidosis

6. A 23-year-old patient complains of red-colored urine, facial swelling over the past 3 days, and decreased urine output over the past day. His examination is notable for blood pressure 130/80 mm Hg, periorbital edema. His urinalysis is remarkable for proteinuria – 0,099 g/l, 100 red blood cells per high-power field, and red blood cell casts. His serum electrolytes are normal. This clinical situation is likely caused by:

A. Acute glomerulonephritis

B. Acute pyelonephritis

C. Nephrotic syndrome

D. Acute renal failure

E. Chronic renal failure

7. Patient 20 years old, is being treated in the Nephrology department, complains of anuria, back pain, headache, nausea. Felt ill 2 days ago. Illness began with pain in the lower back, fever, headache, reduced amount of urine, the appearance of red urine. Two weeks ago, suffered scarlet fever. At the time of inspection BP 170/120 mmHg, HR 90 bpm. In the blood: Hb - 102 g/ l, ESR - 30 mm/h. What is the most probable cause of anuria in this case?

A. Renal amyloidosis

B. Acute pyelonephritis

C. Acute interstitial nephritis

D. Acute glomerulonephritis

E. Urolithiasis

8. 2 weeks after recovering from tonsillitis an 18-year-old patient developed edemas of face and lower limbs. Objectively: the patient is in grave condition, BP - 120/80 mm Hg. Urine is of dark brown colour. Oliguria is present. On urine analysis: specific gravity - 1,015, protein - 1,2 g/l, RBCs are leached and cover the whole vision field, granular casts - 1-2 in the vision field, salts are represented by urates (large quantity). What is the most likely diagnosis?

A. Acute glomerulonephritis with nephritic syndrome

B. Acute glomerulonephritis with nephrotic syndrome

C. Acute glomerulonephritis with nephrotic syndrome, hematuria and hypertension

D. Acute glomerulonephritis with isolated urinary syndrome

E. Nephrolithiasis

9. A 39-year-old patient complains of morning headache, appetite loss, nausea, morning vomi-ting, periodic nasal haemorrhages. The patient had acute glomerulonephritis at the age of 15.

Examination revealed rise of arterial pressure up to 220/130 mm Hg, skin haemorrhages on his arms and legs, pallor of skin and mucous membranes. What biochemical parameter is the most important for making diagnosis in this case?

A. Blood creatinine

B. Blood bilirubin
C. Blood sodium
D. Uric acid
E. Fibrinogen

10. Women 28 y.o. addressed to a doctor with complains of facial oedema, mild peripheral oedema, periodically appearance of red colour urine. In adolescence she had tonsillitis frequently. Objectively: pale skin, T-36,8°C, Ps-68 bmp, rhythmic. BP - 170/110 mmHg. What changes in urine are most expected?

A. Decreasing of relative density and proteinuria
B. Erythrocyturia and uraturia
C. Decreasing of relative density, myoglobinuria
D. Proteinuria, Erythrocyturia, cylindruria
E. Increasing of relative density, hematuria, bacteriuria

Standard answers: 1-C, 2-D, 3-A, 4-C, 5-E, 6-A, 7-D, 8-A, 9-A, 10-D.

An example of the initial examination of the patient

Passport part: Name, European female of 38 years old.

Complaints: lover back pain, face puffiness, «meat slops» urine, high blood pressure, swelling of the ankles, headache.

Medical history: Considers herself ill for about 7 days, when appear
moderate lover back pain and face puffiness, a few days after she observe high blood pressure, swelling of the ankles. She felt better after taking captopril and torasemide. Later, she noticed that the urine became like «meat slops». She suffered acute tonsillitis 12 days before symptoms appeared. Turned to a family doctor for help, was sent to the clinic of the medical university. Hospitalization in the internal medicine department with intensive care beds has been agreed.

Life history: Material and living conditions are satisfactory. From age 6 suffered
from reccurent tonsillitis (1-2 per year). Tuberculosis, venereal disease,
denies. No any allergic reaction to the medications. There were no occupational hazards. Hereditary history is not burdened. Does not smoke, does not abuse alcohol. Gynecological history: there were no pregnancies, no births. She has not been in contact with infectious patients in the last 3 days. She has not left the country for the last 3 years.

Objective status: The general condition of the patient is of moderate severity,
clear consciousness. The physique is correct. The position in bed is active.
The skin and visible mucous membranes are clear, pale. Subcutaneous fat is
developed evenly, with some excess in the abdomen. Nutrition normal. Body mass index = 23 kg/m2. Breathing over the lungs is vesicular, no wheezing. Percussion - clear pulmonary sound. Breath rate - 17 / min. BP –160/90 mm Hg symmetrical on both hands. Heart rhythm is regular, heart rate – 80 beats. in 1 min. Heart sounds are clear. Tongue moist, coated with white bloom. The abdomen is soft and painless on palpation. The liver and spleen are not palpable. The symptom of tapping on the lumbar region is positive on both side. Peripheral edema of feet and ankles, puffy face.

Diagnosis:
Acute post-streptococcal glomerulonephritis, nephrotic syndrome?

Examination plan:

1. Cell blood count,
2. blood biochemistry: creatinine, urea, albumin, antistreptolysin-O
3. coagulation test,

4. liver function tests,
5. lipid profile
6. urinalysis, Nechiporenko`s test;
7. ECG
8. Kidney ultrasound
9. Kidney biopsy
10. Throat culture

Treatment plan:

1. Bed rest, nephrology diet.
2. Methylprednisolone 60 mg / day, i.v. infusion once a day, 7 days, then gradual dose reduction
3. Amoxicillin 500 mg twise a day, 10 days
4. Ramipril 10 mg orally once a day in the morning
7. Torasemide 20 mg orally once a day in the morning

IV. Making conclusions, telling final marks, tasks for the next lesson.

Literature list

- Basic literature source:

1. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases // Kidney inter. – 2021. – Vol. 100, issue 4. Suppl. P.1-276. doi: 10.1016/j.kint.2021.05.021.

2. BMJ Best Practice. Glomerulonephritis. - BMJ publishing group LTD, 2018. – 53 p.

- Additional literature source:

1. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Practice guideline, vol. 99, iss. 3, suppl., s1-s87, march 01, 2021

Practical lessons # 15-16

Topic 9: Pyelonephritis, tubulointerstitial nephritis

Object: To teach applicants to master the method of examination of patients with respiratory diseases with the selection of the main pulmonological syndromes. To study probable etiological factors, pathogenesis of chronic obstructive pulmonary diseases, their main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis and efficiency of patients.

Basic concepts:

№	Term	Definition
1	Bacteriuria	is defined as presence of bacteria in the urine. In quantity not more than 50 000 in 1 ml they may occur in the urine of healthy person. In the presence of bacteriuria, it is important to determine its degree and microorganism sensitivity to various antibiotics.
2	Tubular (renal) epithelium cells	are absent normally in the urine. Their presence indicates acute or chronic affection of the kidneys. They can also be detected in fever, toxicities, and in infectious diseases.
3	Transitional epithelium cells	presence in the urine suggests inflammatory processes in the pelves or bladder.
4	Squamous epithelium cells	originate from genitalia and urethra, and diagnostic their significance is low.
5	Cylinders (casts)	These are cylindrical bodies formed in the lumen of the distal tubule, particularly the collecting tubule. Casts are protein copies of tubules. Appearance of cylinders in urine sediment is called cylinduria - the sign of organic renal diseases.
6	Nechiporenko's method	allows counting formed elements in 1 ml of urine, normally: o Leucocytes – to 4000; o Erythrocytes – to 1000; o Casts – to 200.
7	Zimnitsky's test	characterize condition of renal concentrating and excretory ability. In order to correct measure urinary concentrating ability, the patient must avoid taking much fluid. Urine samples are collected each 3 hours in separate container with designation of time – 8 portions during 24 hours. Volume and specific gravity of the urine is measured in each portion.

Pyelonephritis - a severe infectious inflammatory disease of the renal parenchyma, calices, and pelvis that can be acute, recurrent, or chronic. Acute infections may be caused by enteric bacteria (e.g., *Escherichia coli*) that ascend from the lower urinary tract or that spread haematogenously to the kidney. Most episodes are uncomplicated and are cured with no residual renal damage. Complicated infections can result from underlying medical problems (e.g., diabetes mellitus, HIV), genitourinary anatomical abnormalities, obstruction (e.g., benign prostatic hypertrophy, calculi), and/or multi-drug-resistant pathogens. Urinary tract infection, or UTI, is a non-specific term that

refers to infection anywhere in the urinary tract, from the urethra to the bladder to the ureters to the kidneys. Pyelonephritis refers specifically to infections in the kidney.

AETIOLOGY. The major causative pathogens of acute pyelonephritis are gram-negative bacteria. *Escherichia coli* causes approximately 60% to 80% of uncomplicated infections. Other gram-negative pathogens include *Proteus mirabilis* (responsible for about 15% of infections) as well as *Klebsiella* (approximately 20%), *Enterobacter,* and *Pseudomonas* species. Less commonly, gram-positive bacteria such as *Enterococcus faecalis*, *Staphylococcus saprophyticus,* and *S aureus* may be seen.

Complicated acute pyelonephritis is more common in elderly people, in people with diabetes, and in the immunosuppressed. Organisms differ in these cases and include a broad range of pathogens, many of which are resistant to multiple antibiotic agents and are more likely associated with complicated disease. In older hospitalised patients, because of increased usage of catheters (portals to infection), gram-negative organisms such as *P.mirabilis*, *Klebsiella*, *Serratia*, and *Pseudomonas* are more common aetiologies, and only 60% of cases are due to *E coli*. In people with diabetes, infections are predominantly a result of *Klebsiella*, *Enterobacter*, *Clostridium*, or *Candida*. Those with immunosuppression (e.g., HIV, malignancy, transplantation) are especially prone to silent infections as a result of non-enteric, aerobic, gram-negative rods and *Candida*.

DIAGNOSIS. Fever and chills, flank pain, and irritative voiding symptoms (e.g., urgency, frequency, and dysuria) in a female patient should prompt examination and investigation. Other key symptoms include nausea or vomiting. The triad of flank pain, fever, and nausea and vomiting occurs much more often in patients with pyelonephritis than in those with cystitis.

Physical examination

Temperature greater than 38.0ºC (100.4ºF) is a key finding supporting the diagnosis. In one study, temperature greater than or equal to 37.8ºC (100ºF) was strongly correlated with acute pyelonephritis. Tachycardia may be present. Costovertebral angle tenderness may be pronounced.

Laboratory tests

Initial laboratory tests in all patients with suspected pyelonephritis are urinalysis and urine culture. Urinalysis shows pyuria, bacteriuria, and varying degrees of haematuria. Pyuria is almost invariably present; in fact, its absence should prompt consideration of an alternative diagnosis. WBC casts, if present, suggest a renal origin for the pyuria. A Gram stain performed on spun urine can sometimes help distinguish gram-negative from gram-positive organisms, thus influencing the choice of therapy.

Urine culture (from a clean-catch or catheterised specimen) shows heavy growth of the causative pathogen (classically ≥100,000 colony-forming units [CFUs] per millilitre of voided urine).

Blood cultures are indicated in more severely ill patients. Blood cultures are positive for the causative pathogen in approximately 10% to 20% of women with acute uncomplicated pyelonephritis.

Other initial laboratory tests indicated in the initial work-up are full blood count, erythrocyte sedimentation rate, and serum C-reactive protein. Procalcitonin (a propeptide produced by the monocytes-macrophage cells during bacterial infections) is a more specific diagnostic marker of bacterial infection and values appear to correlate with severity.

Interleukins (IL-6, IL-32), as acute-phase reactants, are also being evaluated as possible markers to distinguish lower urinary tract infections from pyelonephritis. Copeptin is a C-terminal part of pro-vasopressin (CT-pro-AVP) that is released along with vasopressin and has been investigated for use as a diagnostic tool in bacterial infections and sepsis.

Imaging studies

Additional imaging is not usually necessary for diagnosis but can often be useful when subjects are not responding to treatment as expected or after 72 hours. In patients with complicated infections, renal ultrasound may aid diagnosis by identifying hydronephrosis from a stone or other source of obstruction or show intra- or peri-renal fluid collections and cysts.

Contrast-enhanced spiral computed tomography and/or magnetic resonance imaging of the abdomen can further delineate structural abnormalities to help guide therapy. Computed tomography of the abdomen can expose subjects to considerable radiation, but may be easier to schedule and is less expensive than magnetic resonance imaging.

RISK FACTORS.

Strong	Weak
Frequency of sexual intercourse ≥3 times per week in the previous 30 days Risk factor for uncomplicated disease The mechanical action of sexual intercourse may facilitate entry of *Escherichia coli* strains into the bladder.	Mother with UTI history Risk factor for uncomplicated disease
Urinary tract infection (UTI) Risk factor for acute uncomplicated case.	New sex partner Risk factor for uncomplicated disease
Medication-treated diabetes is reported as a risk factor for urinary tract infection in post-menopausal women Increased prevalence of asymptomatic vaginal *E coli* colonisation among post-menopausal women with diabetes who are receiving insulin treatment	Spermicide use May alter the normal lactobacillus-dominant vaginal flora and facilitate *E coli* colonisation of the vagina
Stress incontinence Risk factor for uncomplicated disease	Age between 18 and 50 years Uncomplicated disease is diagnosed most often in adult women
Foreign body in urinary tract (eg. calculus,catheter) Risk factor for complicated cases. Renal stones allow bacteria to remain hidden in the interior of the stone, whereas indwelling catheters may allow bacteria to form a biofilm, which helps resist antibiotic treatment.	Age > 60 years Risk factor for complicated disease. The risk of other medical problems, such as diabetes and enlarged prostate, increases with age.
Anatomical/functional urinary abnormality Risk factor for complicated disease. Such abnormalities include polycystic kidney disease, enlarged prostate, vesicoureteric reflux, ureteroceles, and neurogenic bladder. Anatomical problems such as renal cysts and ureteroceles allow bacteria to remain in hard-to-access locations in the body (e.g., inside cysts).	

Functional abnormalities such as neurogenic bladder and reflux increase likelihood that the kidneys will be exposed to bacteria.	
Immunosuppressive state Risk factor for complicated cases. Immunosuppression can occur to varying degrees, which will determine the kinds of infections that are more likely and the degree of risk associated with these infections. Corticosteroids suppress the entire cytokine and inflammatory cascade, making infections with all agents more likely, whereas only a slight decrease in CD4 count with HIV may not increase infection risk.	
Pregnancy Risk factor for complicated disease. The enlarging uterus compressing the ureters and the increasing laxity of the pelvic support system with the hormonal changes promote the likelihood of obstructive uropathy.	

DIFERENTIAL

Chronic pyelonephritis	Suggested by a relevant history of underlying medical problems, such as anatomical abnormalities that predispose to obstruction (e.g., kidney stones), metabolic factors (e.g., diabetes), or recurrent infections with resistant bacteria that lead to permanent renal damage evident on imaging studies. Imaging studies often show small, irregular, scarred kidneys.
Pelvic inflammatory disease	Determined via a history of sexual intercourse; lower abdominal, pelvic, or low back pain; pain with movements; vaginal discharge; fevers or chills; abdominal or cervical tenderness. Pelvic examination may show vaginitis, urethral discharge, or herpetic ulcerations. Cervical examination may show cervicitis. Cervical cultures can identify causative pathogens (e.g., *Neisseria gonorrhoeae, Chlamydia trachomatis*). Microscopic examination of vaginal discharge demonstrates neutrophils.
Pelvic pain syndrome	Recurrent symptoms, including dysuria, pain on intercourse, and pelvic pain, occur with negative cultures.

	Symptoms that affect primarily the bladder may be associated with a small bladder and frequent voiding. No differentiating tests exist.
Cystitis	Does not display systemic signs or symptoms (e.g., fevers, chills, nausea, vomiting, and back pain). Often associated with dysuria and frequency. No differentiating tests exist.
Acute prostatitis	Can be associated with anal intercourse in men. Symptoms may include dysuria, frequency, and blood in the urine, or may be mild and subacute. May recur in patients who are treated for an adequate duration (up to 3 weeks). Physical examination shows a tender, often enlarged prostate. Microscopic analysis shows WBCs in urine obtained after prostate massage or by collection of the terminal portion of a urine sample.

MANAGEMENT

Indications for hospitalisation include:

- Inability to maintain oral hydration or adherence to the medication regimen
- Hypotension
- Vomiting
- Dehydration
- Sepsis
- High WBC count
- Patients with a temperature 39.0ºC (>102.2ºF)
- Severely ill patients with marked debility or multiple comorbidities
- Pregnancy
- Uncertainty about the diagnosis.

Older and immunocompromised patients, who are at risk for more severe disease, are also usually hospitalised.

Empiric antibiotic choices

Treatment should start before the results of blood or urine cultures are received in patients in whom a high suspicion of infection is present to prevent the patient from deteriorating. The empiric choice of antibiotics should be based on severity of disease, history of prior antibiotic use, and local bacterial susceptibilities.

Because high drug concentrations in the renal medulla are more strongly correlated with cure than serum or urinary drug levels, agents such as aminoglycosides and fluoroquinolones, with high renal tissue levels, may be preferable to beta-lactam antibiotics. Prescription of a reduced dosage of gentamicin in patients with a decline in renal function is advisable. Antimicrobial susceptibility of uropathogens in the community will also guide treatment decisions.

Mild-to-moderate and uncomplicated pyelonephritis

These patients are able to take oral medication and are haemodynamically stable, and other laboratory parameters are essentially normal. Treatment is with oral antibiotics. Possible antibiotic regimens include fluoroquinolones, cephalosporins, and sulphonamides.The Infectious Diseases Society of America recommendations for treatment affirm that the standard 10 to 14 days of outpatient treatment with oral antibiotics is generally sufficient in mild cases. They also agreed that courses of highly active agents (e.g., fluoroquinolones) as short as 7 days may be sufficient for mild or moderate cases in areas where fluoroquinolone resistance is <10%. In areas where fluoroquinolone resistance is >10%, the recommendations suggested adding a one-time intravenous dose of a long-acting antimicrobial such as 1 gram of ceftriaxone or a consolidated 24-hour dose of an aminoglycoside. Routine post-treatment urine cultures in asymptomatic patients are not required.

Severe and complicated pyelonephritis or pregnancy

Pregnant women found to have asymptomatic bacteriuria on screening should be treated to ensure eradication of the bacteria.

Patients with either severe symptoms (not able to take oral medication, volume depleted, early septic haemodynamic parameters, other laboratory parameters may also be abnormal) or complicated disease, and all pregnant patients, should be admitted and treated with intravenous agents. Blood and urine cultures should be obtained. The choice of antibiotic regimen should be based on culture results and local resistance patterns. Possible regimens include fluoroquinolones, extended-spectrum cephalosporins, aminoglycosides with or without ampicillin (if enterococcus is being considered), aminopenicillins, antipseudomonal penicillins, and carbapenems. The European Association of Urology suggests that in communities with >10% *E coli* resistance rates to fluoroquinolones or beta-lactams, aminoglycosides or third-generation cephalosporin be the first choice. Historically, treatment consisted of intravenous antibiotics for 6 weeks. Studies later showed that a 2-week course of therapy was often sufficient for bacteriological cure and improvement of symptoms. With improvement, the patient's regimen can be changed to an oral antimicrobial to which the organism is susceptive to complete the course of therapy.

Complications include obstruction requiring catheterisation, sepsis, renal failure, abscess formation, and antibiotic failure. Follow-up urine cultures are recommended several weeks after completion of treatment, in order to document a bacteriological cure. Pregnant women also generally recover completely with treatment.

Recurrent disease

Recurrence usually occurs within 1 to 2 weeks. The most likely cause of recurrence is insufficient duration of initial treatment. Other possibilities include development of antibiotic resistance or selection for another organism. Repeat urine culture and antimicrobial susceptibility testing is indicated. If, on repeat culture, the bacterial strain and susceptibility profile are the same, a renal ultrasound or computed tomographic scan should be obtained. Retreatment can be with either a longer treatment course of the same antibiotic as used in initial therapy or a different antibiotic treatment.

Mild to moderate symptoms and uncomplicated disease

1-st line: cefixime 400 mg orally OD for 2 weeks OR ciprofloxacin 500 mg orally twice daily for 1-2 weeks

Severe symptoms or complicated disease or pregnant

1-st line: ceftriaxone 1 g i/v OD OR ciprofloxacin 400 mg i/v every 12 hours

Hospitalised patients should show improvement in 48 to 72 hours; if not, consider repeat cultures and/or imaging studies to evaluate other potential infectious aetiologies or anatomical or functional genitourinary pathology interfering with treatment.

The duration of therapy should be adjusted according to the patient's response to treatment.

If gram-positive cocci are causative, treat with ampicillin-sulbactam with or without an aminoglycoside.

With improvement, the patient's regimen can be changed to an oral antimicrobial to which the organism is susceptive to complete the course of therapy.

Gentamicin is classified as FDA category D in pregnancy. It should only be used in pregnant women when the benefits of treatment outweigh the risks. The risks associated with the use of this drug are mainly nephrotoxicity and ototoxicity.

Emerging treatment

- Antioxidant/anti-inflammatory therapies

Some factors of *Escherichia coli* (e.g., adhesins, siderophores, toxins, polysaccharide coatings) in the future may provide effective targets for anti-urinary tract infection interventions (such as cox-2 inhibitors).

- Vaccine therapy

Specific-antigen vaccines are being studied due to advances in protein purification and the development of recombinant DNA technology. Immunising mice with an *E coli* capsular antigen linked to diphtheria toxoid has been shown to improve immunogenicity of the vaccine and increase cell-mediated immune activity in response to subsequent *E coli* exposure.

- Meropenem/vaborbactam

Vaborbactam is a novel beta-lactamase inhibitor. Its combination with meropenem is being developed as a new agent to treat serious gram-negative infections (e.g., complicated urinary tract infection), including infections caused by bacteria resistant to currently available carbapenems. The US Food and Drug Administration (FDA) has approved meropenem/vaborbactam for the treatment of adult patients with complicated urinary tract infection, including pyelonephritis, caused by designated susceptible Enterobacteriaceae (*Escherichia coli*, *Klebsiella pneumoniae*, and *Enterobacter cloacae* species complex).

- Plazomicin

Plazomicin is a next-generation aminoglycoside designed to evade all clinically relevant aminoglycoside-modifying enzymes, the main mechanism of aminoglycoside resistance. It has been approved by the FDA for the treatment of patients 18 years of age or older with complicated urinary tract infections, including pyelonephritis, and bloodstream infections due to certain Enterobacteriaceae in patients who have limited or no alternative treatment options.

PREVENTION

Primary: No vaccines exist for prevention of acute pyelonephritis. There are several methods to prevent urinary tract infections in women, which may help prevent ascending urinary tract infections. These methods are as follows:

- Increase fluid intake to at least 8 glasses per day to maintain bladder hygiene.
- Improve voiding habits by always responding to initial urge to void.
- Void after intercourse to rid urethra of bacteria acquired during sex, and if there is a history of atypical anatomy or recurrent urinary tract infections.

Secondary: Antibiotic prophylaxis may be indicated, specifically cephalosporins, trimethoprim-sulfamethoxazole, and nitrofurantoin. Long-term antibiotics appear to reduce the risk of repeat symptomatic urinary tract infection in susceptible children, but the benefit is small and must be considered together with the increased risk of microbial resistance.

a. Chronic pyelonephritis

Chronic pyelonephritis is a complex renal disorder characterised by chronic tubulointerstitial inflammation and deep segmental cortical renal scarring and clubbing of the pelvic calyces as the papillae retract into the scars. It is an important cause of end-stage renal disease (ESRD). The term

chronic pyelonephritis is sometimes used synonymously with interstitial nephritis, reflux nephropathy, and chronic atrophic pyelonephritis, and encompasses relatively rare but severe variants such as xanthogranulomatous pyelonephritis (XGP) and emphysematous pyelonephritis (EPN).

KEY DIAGNOSTIC FACTORS

- history of vesicoureteral reflux (VUR)
- history of acute pyelonephritis
- history of renal obstruction

OTHER DIAGNOSTIC FACTORS

- female sex
- nausea
- elevated BP

RISK FACTORS

- neurogenic bladder
- acute pyelonephritis
- vesicoureteral reflux
- obstruction

DIAGNOSTIC INVESTIGATIONS

1st investigations to order

- urinalysis: may be normal; dipstick positive for leukocytes, nitrites, blood; microscopic analysis positive for WBCs, RBCs, or bacteria

Haematuria (81.8%) and bacteriuria (90.9%) are more frequent in patients with xanthogranulomatous pyelonephritis than in those with chronic pyelonephritis.

- renal function: elevated creatinine and estimated GFR, reduced creatinine clearance
- urine culture: positive or may be sterile. In patients with indwelling catheters or neurogenic bladders, 10^2 or 10^4 colony-forming units (CFUs)/mL can be considered positive
- electrolyte panel: hyponatraemia; hyperkalaemia; acidosis
- FBC: anaemia; leukocytosis
- Renal ultrasound: small, irregular, scarred kidneys with echogenic parenchyma (typical of chronic irreversible kidney disease); hydronephrosis, renal stones and peri-renal fluid collections
- Kidney-ureter-bladder (KUB) X-ray: renal stones; small or large kidneys; air in renal collecting/parenchymal system
- CT abdomen: obstruction; renal stones; intra- and peri-renal fluid or air collections; and any related anatomical damage or disease in the retroperitoneum or abdomen

Investigations to consider

- MRI abdomen: obstruction; renal stones; intra- and peri-renal fluid, or air collections; and any related anatomical damage or disease in the retroperitoneum or abdomen
- voiding cystourethrography (VCUG): may demonstrate reflux
- renal biopsy

TREATMENT

1st line – *treatment of underlying cause***:** No specific treatment of chronic pyelonephritis is possible; however, patients should have underlying causes (e.g., infection, obstruction) treated appropriately to prevent further damage. In both children and adults, recurrent infections resulting from anatomical abnormalities are a major factor in the development of chronic pyelonephritis and

renal failure. In chronic interstitial nephritis, the primary aetiological factors are vesicoureteral reflux and obstruction

- with xanthogranulomatous pyelonephritis: **nephrectomy and antibiotics**:

ceftriaxone: 1 g intravenously every 24 hours
or
ciprofloxacin: 200-400 mg intravenously every 12 hours
or
gentamicin: 3-5 mg/kg/day intravenously
or
ampicillin/sulbactam: 3 g intravenously every 6 hours
or
piperacillin/tazobactam: 3.375 g intravenously every 6-8 hours
or
imipenem/cilastatin: 250-500 mg intravenously every 6-8 hours
or
ceftazidime/avibactam: 2.5 g intravenously every 8 hours

Urgent urological consultation is essential in the management of these patients.
The main treatment of this chronic destructive inflammatory process is surgical. Medical treatment does not cure this disease, but because most patients are diabetic, good glucose control and treatment of infection with gram-negative cover are recommended.
Because of the destructive nature of the lesions, XGP may be mistaken for renal cell carcinoma on radiological images (e.g., CT scan). The correct diagnosis may not be made until the patient undergoes surgery.

- with emphysematous pyelonephritis: percutaneous drainage, antibiotics, and supportive therapy

percutaneous drainage ***or*** stent placement AND ceftriaxone: 1 g intravenously every 24 hours

or ciprofloxacin: 200-400 mg intravenously every 12 hours
or gentamicin: 3-5 mg/kg/day intravenously
or ampicillin/sulbactam m: 3 g intravenously every 6 hours
or piperacillin/tazobactam: 3.375 g intravenously every 6-8 hours
or imipenem/cilastatin: 250-500 mg intravenously every 6-8 hours
or ceftazidime/avibactam: 2.5 g intravenously every 8 hours
If no clinical improvement is noted within 24 to 48 hours, a repeat CT scan should be obtained, and nephrectomy considered.

PREVENTION

PRIMARY: Mainstays of preventive therapy include treatment of acute infections and possibly surgical correction of anatomical abnormalities.
Xanthogranulomatous pyelonephritis (XGP) is an uncommon disease with no clear primary prevention strategies; treatment of renal stones, obstruction, and infection is recommended. Emphysematous pyelonephritis is extremely rare and, as with XGP, no clear primary prevention strategies exist; treatment of renal stones, obstruction, and infection is recommended.
SECONDARY: For patients with recurrent infections, a high index of suspicion for infection and rapid treatment is important. Diet and glucose control is recommended in patients with diabetes.
COMPLICATIONS:

- ✓ acute renal failure
- ✓ hyperparathyroidism
- ✓ obstruction
- ✓ chronic kidney disease

Acute interstitial nephritis is a pattern of acute renal inflammation, usually triggered by medications, which is localised to the renal interstitium (the area between the tubules, glomeruli, and blood vessels).

DIAGNOSIS

The classic presentation is of non-oliguric acute renal failure with rash, fever, and eosinophilia (the 'hypersensitivity triad') triggered by a medication. Acute interstitial nephritis (AIN) should be suspected in all patients who develop non-oliguric acute renal failure, and particularly those taking multiple medications. Other causes of acute renal failure, including acute tubular necrosis, acute glomerulonephritis, and acute vascular changes, should be excluded. Referral to a nephrology specialist is advisable with significant acute renal failure.

Clinical assessment

Patients present with non-oliguric acute renal failure. Many patients will also have rash, fever, or eosinophilia of the peripheral blood, but few will have all 3 at the time of presentation.

Arthralgia is sometimes seen as an associated symptom.

Trigger

Over 100 medications are known to trigger AIN; the use of any of these should raise suspicion of AIN. Antibiotics, particularly beta-lactams, are the most common offenders. Almost all penicillins and cephalosporins, many sulfonamides, rifampicin, and a variety of quinolones are known triggers. Other triggers include diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, antihistamines (cimetidine and ranitidine), allopurinol, phenindione, phenytoin, sulfadiazine, mesalazine, and warfarin. Erythromycin, polymyxin, aciclovir, foscarnet, and vancomycin trigger tubulo-interstitial nephritis, a variant of AIN.

Uncommonly, patients with Sjogren's syndrome, sarcoidosis, IgG4-related syndrome, and SLE can also develop AIN. Patients with AIN occurring as part of the tubulo-interstitial nephritis with uveitis (TINU) syndrome will also have uveitis; this is extremely rare.

Clinical examination is usually unremarkable. Pyrexia is a common sign. The associated rash is usually macular or maculopapular. Costovertebral angle tenderness may be present in some patients. NSAIDs trigger a unique reaction consisting of AIN with a concurrent nephrotic syndrome; these patients develop oedema secondary to hypoalbuminaemia. The site of oedema is influenced by posture and is typically periorbital in the morning and pedal in the evening.

Initial investigations

Blood tests

- Serum urea and serum creatinine are required to detect and assess the severity of acute renal failure.
- FBC with WBC differential reveals significant eosinophilia in some cases.
- Anti-neutrophil cytoplasmic antibody (ANCA), anti-nuclear antibody (ANA), extractable nuclear antigens (ENAs), and complement profile if associated systemic disease suspected. ANCA is associated with systemic vasculitis, and ANA and ENA are associated with systemic lupus erythematosus.

Urinalysis

- Usually shows microhaematuria with sterile pyuria (leukocytes with a negative urine culture for bacteria).
- Absence of RBC casts excludes acute glomerulonephritis.
- Once infection is excluded, Hansel's or Wright's staining is required to detect eosinophilia: the staining shows clusters of binucleated eosinophils.
- Heavy proteinuria suggests the presence of nephrotic syndrome. If the patient has nephrotic syndrome but is not taking NSAIDs, other causes should be investigated.

Trial of discontinuation of offending medication

- Symptoms usually resolve following discontinuation of the offending medication; a retrospective diagnosis of AIN can be made if this occurs.
- If symptoms do not resolve, other diagnoses should be excluded.

Subsequent investigations

Renal biopsy

- Provides a definitive diagnosis, but is reserved for patients who have not responded to discontinuation of the triggering medication or who have a relative contraindication to corticosteroid use.
- Requires a careful risk-benefit assessment in consultation with a nephrologist.
- Typical findings are of an interstitial or tubulo-interstitial inflammatory infiltrate with variable numbers of eosinophils, lymphocytes, and plasma cells, with no bacteria, fungi, or other organisms found on special stains of the biopsy.
- If nephrotic syndrome is present, the pattern is usually minimal change disease, although membranous nephropathy has also been reported.

Renal ultrasound

- Shows large swollen kidneys that are often echogenic due to the inflammatory interstitial infiltrates.
- Main use is to exclude hydronephrosis, renal calculi, or shrunken kidneys (a sign of chronic renal failure).

Gallium scan

- Can be used to detect AIN, but findings are non-specific.
- Probably more useful when negative to exclude the diagnosis.

Renal blood flow scans or magnetic resonance angiography

- Can be used to exclude large-vessel vascular lesions such as emboli or renal vein thrombosis.

MANAGEMENT

Treatment depends on the underlying cause. Most cases are caused by medication, but acute interstitial nephritis (AIN) can also occur in the context of chronic inflammatory disease. In general, advice should be sought from a nephrologist, and patients who do not rapidly respond (in <1 week) to the withdrawal of the underlying cause should be referred to a nephrologist for prompt treatment and to exclude other diagnoses, especially where a renal biopsy is indicated.

Medication related

The initial treatment of suspected or confirmed AIN is discontinuation of the offending medication. Most patients will have resolution of their acute renal failure and a progressive return of renal function. If the patient is taking several known offending medications, it will not be clear which medication is the cause. In this situation, all medications should be switched to drugs from a different class. For example, a penicillin would be changed for a quinolone rather than a cephalosporin, and omeprazole would be changed for sucralfate rather than lansoprazole.

Supportive care includes attention to fluid and electrolyte balance. All patients should have serum electrolytes, urea, and creatinine monitored daily during the acute episode. Sodium and volume restriction may be required, along with limitation of potassium and phosphorus intake. Diuretics may be required for treatment of fluid retention. If a diuretic is suspected as the trigger, a diuretic from a different class should be used. Dialysis may be needed in severe cases, but this is usually a temporary supportive measure; most patients will recover sufficient renal function to come off dialysis.

Corticosteroid therapy has been suggested to improve the rate and extent of renal recovery, although there is limited evidence that corticosteroids affect the final outcome. Randomised controlled trials have not yet confirmed the use of corticosteroids, although delay in using them (up to 1 month after diagnosis) in patients who are not rapidly improving does appear to result in worse long-term renal impairment. A short course of prednisolone should be considered in most patients, unless corticosteroid therapy is contraindicated, if there has not been a significant reduction in their

creatinine following withdrawal of the offending agent. This should ideally be undertaken with the results of a renal biopsy confirming the diagnosis of AIN and excluding other possible diagnoses, unless contraindicated for other reasons. If patients relapse on withdrawal of corticosteroid treatment, a repeat course should be given. A few patients have recurrence of renal failure every time corticosteroid therapy is discontinued; these patients are corticosteroid dependent and will require long-term treatment.

Chronic inflammatory disease related

Corticosteroids are the preferred therapy for interstitial nephritis associated with Sjogren's syndrome, sarcoidosis, IgG4-related syndrome, SLE, and tubulo-interstitial nephritis with uveitis (TINU) syndrome. Patients with chronic inflammatory disease may also be taking known triggering medications, and these should be discontinued. Supportive care is the same as for medication-related episodes (monitoring of electrolytes and renal function, sodium and volume restriction, diuretics, dialysis if needed). If patients relapse on withdrawal of corticosteroid treatment, a repeat course should be given. A few patients have recurrence of renal failure every time corticosteroid therapy is discontinued; these patients are corticosteroid dependent and will require long-term treatment.

SECONDARY PREVENTION

The most important preventative action is to avoid exposure to the trigger of the acute episode. If the offending medication has clearly been identified, then avoiding future use of the medication is recommended, because acute interstitial nephritis may recur on re-exposure to the original antigen. Where known cross-reactivity exists, for example between penicillins and cephalosporins, the risk of using a related agent should be carefully weighed up against the benefit of using it. If such an agent is used, the patient should be appropriately monitored for any adverse effects. For the few patients who have chronic inflammatory diseases such as Sjogren's syndrome, sarcoidosis, or SLE, adequate control of the underlying condition is important.

MONITORING

The most important preventative action is to avoid exposure to the trigger of the acute episode. If the offending medication has clearly been identified, then avoiding future use of the medication is recommended, because acute interstitial nephritis may recur on re-exposure to the original antigen. Where known cross-reactivity exists, for example between penicillins and cephalosporins, the risk of using a related agent should be carefully weighed up against the benefit of using it. If such an agent is used, the patient should be appropriately monitored for any adverse effects. For the few patients who have chronic inflammatory diseases such as Sjogren's syndrome, sarcoidosis, or SLE, adequate control of the underlying condition is important.

COMPLICATIONS

- ✓ Corticosteroid-dependent interstitial nephritis: Some patients have recurrence of renal dysfunction every time corticosteroids are withdrawn. These patients are corticosteroid dependent and require long-term corticosteroid therapy.Corticosteroid adverse effects can be a significant source of morbidity in these patients.
- ✓ Chronic renal failure: Most patients with acute interstitial nephritis are left with a small degree of renal impairment as a residual of the prior renal insult; the impairment is usually clinically insignificant and does not progress. Some patients may progress to chronic kidney disease. All patients require annual monitoring. If disease progression is detected, treatment with angiotensin-converting enzyme (ACE) inhibitors may be required.
- ✓ Hypertension.

Equipment: class room, 6-channel ECG machine CARDIOLINE 100 L and Cardioline 200 + II S, ultrasound system

Mylab Six CristaLine with 3 detectors.

Lesson time: 4 hours

Plan

I. Organization moments (Greeting, head count, theme announce, aim of lesson, motivating applicants to study the topic).
II. Control of basic knowledges (The task source for self-knowledge skills tests from «KROK2» - additional materials, checking workbooks)

II.1 Requirements for theoretical readiness of applicants to perform practical classes.

Requirements to knowledges:
- Definition of pyelonephritis and tubulointerstitial nephritis
- Modern aspects of etiology and pathophysiology of pyelonephritis and tubulointerstitial nephritis
- Classification of pyelonephritis and tubulointerstitial nephritis
- Clinical manifestation of pyelonephritis and tubulointerstitial nephritis Laboratory and instrumental investigation of pyelonephritis and tubulointerstitial nephritis
- Carry out differential diagnosis of pyelonephritis and tubulointerstitial nephritis
- Complications of pyelonephritis and tubulointerstitial nephritis
- Treatment, rehabilitation of patients with pyelonephritis and tubulointerstitial nephritis
- Prognosis and disability of patients with pyelonephritis and tubulointerstitial nephritis

List of didactic units
- To get a detailed anamnesis
- To do physical examination of patient, to diagnose and to estimate changes in condition
- To make a plan of additional investigation and estimate it
- Justify and make a preliminary and clinical diagnoses of pyelonephritis and tubulointerstitial nephritis.
- Basic principles of treatment pyelonephritis and tubulointerstitial nephritis.
- Estimation of exacerbation of chronic pyelonephritis and tubulointerstitial nephritis and its treatment
- Estimation of clinical examination, CBC, blood tests, urinalysis, Nechiporenko`s test, Zimnitsky`s test, kidney ultrasound.

II.2 Questions (MSQ, clinical cases) for basic knowledge examination of topic

1. The patient 28 years. Complaints of pain in the lumbar area from the left side, cloudy urine, which appeared 1 day after overcooling. An objective examination: T $37,7^0$ C, pain in lumbar region during stabbing. Laboratory tests: a general analysis of urine protein 1.0 g / l, RBC 5-7 in f/v, WBC 50-80 in f/v., gravity 1014; biochemical tests: protein 65 g/l, creatinine 85 mcmol/l, urea 7,5 mmol/l; CBC — WBC $11x10^9$ What the diagnosis is more likely?
A. Acute glomerulonephritis
B. Chronic glomerulonephritis
C. Acute renal falure
D. Amyloidosis
E. Acute pyelonephritis +
2. Patient 48 years, nephrotic syndrome was diagnosed. Complaints on general weakness, edema. During examination BP 90/60 mmHg, petechial paraorbital elements, macroglossia. Laboratory tests: a general analysis of urine protein 6.5 g / l, RBC 5-9 in f/v, WBC 3-4 in f/v., gravity 1023; biochemical tests: protein 45 g/l, creatinine 95 mcmol/l, urea 7,5 mmol/l, cholesterol 5,1 mmol/l. What the diagnosis is more likely?
A. Pyelonephritis
B. Glomerulonephritis

C. Amyloidosis +
D. Renal failure
E. Chronic tubulointerstitial nephritis
3. Patient 53 years, complaints: pain in lumbar region, fever to 38^0 C, pain during urination. In the history urolithiasis. Objective: BP 150/100 mm Hg, pain during stabbing on lumbar region. Laboratory tests: a general analysis of urine protein 1.5 g / l, RBC 15-20 in f/v, WBC entirely in f/v., gravity 1023; biochemical tests: protein 65 g/l, creatinine 95 mcmol/l, urea 7,5 mmol/l, cholesterol 5,1 mmol/l. What the diagnosis is more likely?
A. Chronic pyelonephritis, exacerbation
B. Glomerulonephritis
C. Cystitis
D. Urolithiasis, complicated pyelonephritis +
E. Tubulointerstitial nephritis
4. Patient 34 years, Complaints of pain in the lumbar area from the left side, cloudy urine, which appeared 1 day after overcooling. An objective examination: T $37,7^0$ C, pain in lumbar region during stabbing. Laboratory tests: a general analysis of urine protein 1.0 g / l, RBC 5-7 in f/v, WBC 50-80 in f/v., gravity 1014; biochemical tests: protein 65 g/l, creatinine 85 mcmol/l, urea 7,5 mmol/l; CBC — WBC $11x10^9$. What is the drug of choice?
A.Prednisolone 1 mg/kg/day
B. Amycacine
C. Cyprofloxacine +
D. Ampicilline
E. Paracetamol
5. Patient 48 years, nephrotic syndrome was diagnosed. Complaints on general weakness, edema. During examination BP 90/60 mmHg, petechial paraorbital elements. Laboratory tests: a general analysis of urine protein 8.5 g / l, RBC 15-20 in f/v, WBC 3-4 in f/v., gravity 1023; biochemical tests: protein 45 g/l, creatinine 95 mcmol/l, urea 7,5 mmol/l, cholesterol 8,1 mmol/l. . What is the best method of diagnosis to determine the future treatment strategy?
A. US of kidneys
B. Excretory urography
C. Dinamic renoscintigraphy
D. Renal biopsy +
E. Zimnitskiy test
6. Patient 23 years, pain in lumbar region, fever to 38^0 C, pain during urination. Objective: BP 130/90 mm Hg, pain during stabbing on lumbar region. Laboratory tests: a general analysis of urine protein 1.5 g / l, RBC 15-20 in f/v, WBC entirely in f/v., gravity 1023; biochemical tests: protein 65 g/l, creatinine 95 mcmol/l, urea 7,5 mmol/l, cholesterol 5,1 mmol/l. Kidney ultrasound — no pathology. What the diagnosis is more likely?
A. Amyloidosis
B. Non complicated pyelonephritis +
C. Complicated pyelonephritis
D. Glomerulonephritis
E. Acute cystitis.
7. Patient 43 years, complaints on general weakness, joint pain, erythematous skin rash. A few days ago took medicines, what drugs - did not remember. Objective: swelling of lower extremities, BP 130/90 mm Hg. Laboratory tests: a general analysis of urine protein 2.5 g / l, RBC 10-15 in f/v, WBC 3-4 in f/v., gravity 1010; biochemical tests: protein 68 g/l, creatinine 135 mcmol/l, urea 7,5 mmol/l, cholesterol 4,1 mmol/l. Kidney ultrasound — no pathology. What the diagnosis is more likely?
A. Complicated pyelonephritis
B. Amyloidosis
C. Acute glomerulonephritis

D. Acute tubulointerstitial nephritis +
E. Chronic renal failure
8. Patient 23 years, pain in lumbar region, fever to 38^0 C, pain during urination. Objective: BP 130/90 mm Hg, pain during stabbing on lumbar region. Laboratory tests: a general analysis of urine protein 1.5 g / l, RBC 15-20 in f/v, WBC entirely in f/v., gravity 1023; biochemical tests: protein 65 g/l, creatinine 95 mcmol/l, urea 7,5 mmol/l, cholesterol 5,1 mmol/l. What is the best method of diagnosis to determine the future treatment strategy?
A. US of kidneys
B. Excretory urography
C. Renoscintigraphy
D. Bacterial urine test +
E. Zimnitskiy test
9. The patient 34 years. Complaints of pain in the lumbar area from the left side, cloudy urine, which appeared 1 day after overcooling. An objective examination: T $37,7^0$ C, pain in lumbar region during stabbing. What changes do you expect to find in the laboratory investigation?
A. Proteinuria 3,5 g/l, hematuria
B. Proteinuria 1,5 g/l, leycocyturia, leycocytosis +
C. Proteinuria 3,5 g/l, hypoproteinemia, hypercholesterolemia
D. Hyperpotassiumemia, creatininemia 150 mcmol/l
E. Hyperpotassiumemia, hematuria, cylinduria
10. Patient 33 years old hospitalized with the diagnosis Chronic renal Disease I stage. Amyloidosis. Nephrotic syndrome. What changes do you expect to find during investigation?
A. Hypopotassiumemia
B. Hypoproteinemia +
C. Anemia
D. Hypeprotassiumemia
E. Hyperglicemia.

III. Proffesional skills formation (skills of patient`s management, treatment)
Professional algorithms: work with a patient (according to patients-students conversation algorithm).

Task 1
Collecting complains, anamnesis, examination of patients
Identify clinical and instrumental symptoms
Make a syndrome based on symptoms
Identify the leading clinical syndrome
Assign laboratory and instrumental examination (CBC, urine analysis, blood tests, Nechiporenko test, Zimnitsky`s test, ECG, EchoCG and others)
Carry out differential diagnosis with glomerulonephritis, cystitis
Make a clinical diagnosis
Determine a degree of disability
Task 2
Prescribing different variants of treatment according to guidelines
Task 3
Work in Internet, work with thematic literature in department library room.
Student must fill patient examination protocol (example is added).

Control materials for final part of the lesson:

1. A 54-year-old male patient complains of aching pain in the lumbar region, that is getting worse after standing in an upright position, physical exercise, supercooling. The patient also reports of

experiencing weakness in the afternoon. Pain in the lumbar region, said about 10 years old. Objectively: pale skin, t- 37,2°C, AP- 180/100 mm Hg, minor costovertebral angle tenderness (Pasternatsky symptom). In blood: RBCs - 3,5X 10^{12}/l, WBCs - 6,5 X 10^{9}/l, , ESR - 22 mm/h. In urine: the relative density - 1010, leukocytes - 12-15 in the field of vision, erythrocytes - 2-3 in the field of vision. Urine bacterial count - 100000 in 1 ml.
What is the most likely diagnosis?
A.Chronic pyelonephritis
B.Nephrolithiasis
C.Polycystic renal disease
D.Chronic glomerulonephritis
E.Amyloidosis
2. A 29 y.o. woman is critically ill. The illness is presented by high fever, chills, sweating, aching pain in lumbar area, discomfort during urination and frequent voiding. Pasternatsky's sign is positive in both sides. On lab examination: WBC- 20*10^{9}/L; on urine analysis: protein - 0,6 g/L, leukocyturia, bacteriuria. Your preliminary diagnosis.
A . Acute glomerulonephritis
B. Exacerbation of chronic pyelonephritis
C. Acute pyelonephritis
D. Acute cystitis
E. Nephrolithiasis
3. A 16 year old girl suddenly got arthralgia, headache, nausea, vomiting; pain and muscle tension in the lumbar area; body temperature rose up to 38-39°C. Pasternatsky's symptom was distinctly positive on the right. In the urine: bacteriuria, pyuria. What is the most probable diagnosis?
A. Acute pyelonephritis
B. Renal colic
C . Acute glomerulonephritis
D. Pararenal abscess
E. Cystitis
4. A 46 y.o. patient complains of colicky pain in the right lumbar region that is irradiating to the lower part of abdomen, nausea. She didn't have such pains before. Survey radiograph of abdominal cavity organs didn't reveal any pathological stains. Ultrasonic sonogram revealed in the enlarged right renal pelvis a hyperechoic mass approximately 1,5 cm large that gives rise to an "ultrasonic track". What is the most probable diagnosis?
A. Benign tumor of kidney
B. Renal calculus
C. Renal cyst
D. Renal tuberculosis
E. Malignant tumor of kidney
5. A 32 y.o. woman has been suffering for 7 months from pain in lumbar region, low grade fever, frequent urination. Urine analysis: moderate proteinuria, leukocytes occupy the whole field of sight, bacteriuria. Blood analysis: leukocytosis, increased ESR. What is the most probable diagnosis?
A . Urolithiasis
B. Acute glomerulonephritis
C. Chronic glomerulonephritis
D. Acute pyelonephritis
E. Chronic pyelonephritis
6. A 22 year old female patient complains about frequent and painful urination, urge to urinate at night, enuresis, pain in the suprapubic and lumbar area. Her urine often has beer coloring. She got married a month ago. Objectively: general state is satisfactory. Lung examination revealed vesicular respiration. Heart sounds are rhythmic, heart rate is 78/min, AP- 128/68 mm Hg. Abdomen is soft, painful in the suprapubic area. Urine contains 12-18 erythrocytes and 12-15 bacteria within eyeshot. What is the most probable diagnosis?

A . Infection of inferior urinary tracts - cystitis
B. Urolithiasis
C. Infection of superior urinary tracts - pyelonephritis
D. Gonorrhoea
E. Primary syphilis
7. A 35-year-old man complains about intense lumbar pain irradiating to the inguinal area, external genitalia, thigh; frequent urination, chill, nausea, vomiting. Objectively: positive Pasternatsky's symptom. Urine analysis revealed that RBCs and WBCs covered the total field of microscope; the urine exhibited high protein concentration. These clinical presentations were most likely caused by the following pathology:
A . Renal infarct
B. Cholelithiasis, biliary colic
C . Urolithiasis, renal colic
D. Intestinal obstruction
E. Osteochondrosis, acute radicular syndrome
8. Patient 39 years old complains of attack pain in the right lumbar region with irradiation to the right iliac area. Several years ago urolithiasis and gallsone disease were diagnosed. Status – moderate gravity, dry skin. Ortner's symtom – negative, symptom of stabbing on lumbar region – positive from the right. The most appropriate method of treatment is:
A . Emergency seance of hemodialysis
B. Antispasmodic and Analgesics intake
C. Peritoneal dialysis
D. Two antibiotics parenterally
E. Laparoscopic cholecystectomy
9. A 45-year-old male patient complains of acute pain in his right side irradiating to the right thigh and crotch. The patient claims also to have frequent urination with urine which resembles a "meat slops"in color. The patient has no previous history of this condition. There is costovertebral angle tenderness on the right (positive Pasternatsky's symptom). What is the most likely diagnosis?
A. Urolithiasis
B. Acute appendicitis
C. Acute pyelonephritis
D. Acute cholecystitis. Renal colic
E. Acute pancreatitis
10. A 58-year-old patient complains of general weakness, weight loss up to 10 kg within the last 1,5 months, progressive pain in the small of the back, raise of blood pressure to 220/160 mm Hg, subfebrile body temperature. Objectively: tuberous slightly movable lump can be palpated in the right subcostal area; veins of spermatic cord and scrotum are dilated. Blood test: Hb - 86 g/l, ESR - 44 mm/h. Uri-ne test: specific gravity - 1020, proteine - 0,99 g/l, erythrocytes - all field of vision, leukocytes - 4-6 in the field of vision. The provisional diagnosis is:

A. Urolithiasis
B. Acute pyelonephritis
C. Kidney tumor
D. Acute glomerulonephritis
E. Nephroptosis
Standard answers: 1-A, 2-C 3-A, 4-B, 5-E, 6-A, 7-C, 8-B, 9-A, 10-C

B. Clinical case with answers

Patient 25 years, with 17 years diagnosed with polycystic kidney, chronic pyelonephritis. Admitted to the hospital with complaints of weakness, headaches, periodical temperature rises with chills, the last 2 months there were nausea, vomiting, diarrhea.

OBJECTIVE: Skin and visible mucous are pale. Face puffy, his eyelids were oedematous. RR - 18 to 1 minute. Vesicular breathing. Heart sounds are rhythmic, muffled. BP - 165/105 mmHg. Abdomen palpation soft, painless, liver and spleen were not palpable. Stabbing on lumbar region – no pain. A slight pasty legs and feet.
Urine: 1008-protein 0,6 g / l, L.-20-30 in the field of view, E. 1-2 in the field of view, the cylinders hyaline-5-6 in the field of view, the bacteria-cocci, a significant number . Blood test: Hb-96 g / l, L-3,4 × 10^{12}/l.L. - 8.6 × 10^{9} / l, ESR - 24 mm / hour. Urea - 14.2 mmol / l, creatinine - 0.136 mmol / l, GFR - 72 ml / min.
1. Primary clinical diagnosis.
2. Plan of additional investigation
3. Treatment.
Answering standards
1. CKD II. Polycystic kidneys. Secondary chronic pyelonephritis, exacerbation. Symptomatic renal hypertension II stage. Secondary anemia.
2. Nechiporenko, Zimnitskiy tests, the definition of bacteriuria, acid-base balance, control of daily diuresis, total protein and protein fractions, lipidogramme, coagulation, renal ultrasound, consulting ophthalmologist, ECG.
3. Bed regime, a table number 7 with the restriction of protein, antibiotic therapy, sorbent, intestinal dialysis, sodium bicarbonate, dis intoxication, antianemic, antihypertensive therapy.

IV. Making conclusions, telling final marks, tasks for the next lesson

Literature list

- Basic literature source:

1. Harrison's Manual in Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 1245 p.

2. Harrison's Principles of Internal Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 3528 p.

3. BMJ Best Practice. Acute interstitial nephritis. - BMJ publishing group LTD, 2017. – 29 p.

4. BMJ Best Practice. Acute pyelonephritis. - BMJ publishing group LTD, 2018. – 45 p.

- Additional literature source:

1. European Association of Urology. Guidelines on urological infections. 2019 [internet publication].

2. KDIGO 2021 Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Practice guideline, vol. 99, iss. 3, suppl., s1-s87, march 01, 2021

https://www.kidney-international.org/article/S0085-2538(20)31270-9/fulltext

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European male of 28 years old.

Complaints: pain in right lumbar area, nausea, vomiting, weakness, fatigue, accompanied by headache, an increase in body temperature up to 39.2 C.

Medical history: According to the patient, the condition worsened about 3 days ago, when, after a cold he started to feel chills. After several hours patient starts to feel fatigue. On next day he mentioned that he had a headache and ***:*** pain in right lumbar area, his urine started to be cloudy. At the present time patient went to the clinic in connection with the persisting complaints described above. Hospitalization is strongly recommended.

Life history: Patient doesn't have any another pathology.

Allergic history is not burdened.

Hereditary history: mother suffers from chronic cystitis.

Epidemiological anamnesis: Hepatitis, tuberculosis, malaria, helminthiasis, candidiasis, blood transfusion for the last 3 months, the passage of the segments of the worms denies. He has not been abroad for the last 12 months.

Bad habits: denies

Objective status: General condition of moderate severity. Hypersthenic constitution, satisfactory nutrition. Height 172 cm Weight - 88 kg.

The skin and visible mucous membranes are clean, pale pink.

The thyroid gland and peripheral lymph nodes are not enlarged.

Breathing over the lungs is vesicular, no wheezing. Percussion - clear pulmonary sound. Breath rate = 18 / min.

BP –130/80 mm Hg symmetrical on both hands. Heart rhythm is regular, heart rate – 87 beats. in 1 min. Heart sounds are clear.

Tongue moist, coated with white bloom. The abdomen is soft and painless on palpation. The liver and spleen are not palpable.

The symptom of tapping over the projection of the kidneys is positive on right side. No peripheral edema.

Diagnosis: Acute pyelonephritis

Examination plan:

1. Cell blood count,
2. blood biochemistry: creatinine, urea
3. coagulation test,
4. liver function tests,
5. lipid profile
6. urinalysis, Nechiporenko`s test;
7. Kidney ultrasound
8. ECG,

Treatment plan:

1. Bed rest, nephrologic diet with a reduction of protein and salt
2. Cefpodoxim 200 mg, orally, in morning and in the evening, after meal
3. Omeprazole 20 mg 2 times a day, orally, before breakfast and before lunch
4. Caps. «Diurol» orally, in morning and in the evening, after meal
5. Paracetamol 1000 mg intravenous 1 time per day

Practical lessons # 17-18
Topic 10: Chronic kidney disease

Object: To teach applicants to master the method of examination of patients with nephrology diseases with the selection of the main syndromes. To study probable etiological factors, pathogenesis of chronic kidney disease, main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis and efficiency of patients.

Basic concepts:

№	Term	Definition
1	Glomerular filtration rate (GFR)	the volume of fluid filtered from the renal (kidney) glomerular capillaries into the Bowman's capsule per unit time.
2	Oliguria	the low output of urine specifically more than 50 ml/day but less than 500ml/day.
3	Anuria	nonpassage of urine or passage of less than 50 milliliters of urine in a day.
4	Dialysis	procedure to remove waste products and excess fluid from the blood when the kidneys stop working properly.
5	Hyperkalemia	an elevated level of potassium (K+) in the blood with levels above 5.5 mmol/l Hyperkalemia can cause an abnormal heart rhythm which can result in cardiac arrest and death.
6	Erythropoietin	a glycoprotein cytokine secreted mainly by the kidney in response to cellular hypoxia; it stimulates red blood cell production (erythropoiesis) in the bone marrow.

Chronic kidney disease (CKD) is long-standing, progressive deterioration of renal function. Symptoms develop slowly and include anorexia, nausea, vomiting, stomatitis, dysgeusia, nocturia, lassitude, fatigue, pruritus, decreased mental acuity, muscle twitches and cramps, water retention, undernutrition, peripheral neuropathies, and seizures. Diagnosis is based on laboratory testing of renal function, sometimes followed by renal biopsy. Treatment is primarily directed at the underlying condition but includes fluid and electrolyte management, erythropoietin for anemia, and often dialysis or transplantation.

Etiology
CKD may result from any cause of renal dysfunction of sufficient magnitude (see Table: Major Causes of Chronic Kidney Disease). The most common causes in the US are diabetic nephropathy, followed by hypertensive nephrosclerosis and various primary and secondary glomerulopathies. Metabolic syndrome, in which hypertension and type 2 diabetes are present, is a large and growing cause of renal damage
Pathophysiology
CKD can be roughly categorized as diminished renal reserve, renal insufficiency, or renal failure (end-stage renal disease). Initially, as renal tissue loses function, there are few abnormalities because the remaining tissue increases its performance (renal functional adaptation); a loss of 75% of renal tissue causes a fall in GFR to only 50% of normal.
Decreased renal function interferes with the kidneys' ability to maintain fluid and electrolyte homeostasis. Changes proceed predictably, but considerable overlap and individual variation exist. The ability to concentrate urine declines early and is followed by decreases in ability to excrete

phosphate, acid, and potassium. When renal failure is advanced (GFR ≤ 10 mL/min/1.73 m^2), the ability to dilute urine is lost; thus, urine osmolality is usually fixed close to that of plasma (300 to 320 mOsm/kg), and urinary volume does not respond readily to variations in water intake.

Creatinine and urea

Plasma concentrations of creatinine and urea (which are highly dependent on glomerular filtration) begin a hyperbolic rise as GFR diminishes. These changes are minimal early on. When the GFR falls below 10 mL/min/1.73 m^2 (normal = 100 mL/min/1.73 m^2), their levels increase rapidly and are usually associated with systemic manifestations (uremia). Urea and creatinine are not major contributors to the uremic symptoms; they are markers for many other substances (some not yet well defined) that cause the symptoms.

Sodium and water

Despite a diminishing GFR, sodium and water balance is well maintained by increased fractional excretion of sodium and a normal response to thirst. Thus, the plasma sodium concentration is typically normal, and hypervolemia is infrequent unless dietary intake of sodium or water is very restricted or excessive. Heart failure can occur due to sodium and water overload, particularly in patients with decreased cardiac reserve.

Potassium

For substances whose secretion is controlled mainly through distal nephron secretion (eg, potassium), adaptation usually maintains plasma levels at normal until renal failure is advanced. Potassium-sparing diuretics, ACE inhibitors, beta-blockers, NSAIDs, cyclosporine, tacrolimus, trimethoprim/sulfamethoxazole, pentamidine, or angiotensin II receptor blockers may raise plasma potassium levels in patients with less advanced renal failure.

Calcium and phosphate

Abnormalities of calcium, phosphate, parathyroid hormone (PTH), and vitamin D metabolism and renal osteodystrophy can occur. Decreased renal production of calcitriol contributes to hypocalcemia. Decreased renal excretion of phosphate results in hyperphosphatemia. Secondary hyperparathyroidism is common and can develop in renal failure before abnormalities in calcium or phosphate concentrations occur. For this reason, monitoring PTH in patients with moderate CKD, even before hyperphosphatemia occurs, has been recommended.

Renal osteodystrophy (abnormal bone mineralization resulting from hyperparathyroidism, calcitriol deficiency, elevated serum phosphate, or low or normal serum calcium) usually takes the form of increased bone turnover due to hyperparathyroid bone disease (osteitis fibrosa) but can also involve decreased bone turnover due to adynamic bone disease (with increased parathyroid suppression) or osteomalacia. Calcitriol deficiency may cause osteopenia or osteomalacia.

pH and bicarbonate

Moderate acidosis (plasma bicarbonate content 15 to 20 mmol/L) is characteristic. Acidosis causes muscle wasting due to protein catabolism, bone loss due to bone buffering of acid, and progression of kidney disease.

Anemia

Anemia is characteristic of moderate to advanced CKD (≥ stage 3). The anemia of CKD is normochromic-normocytic, with an Hct of 20 to 30% (35 to 40% in patients with polycystic kidney disease). It is usually caused by deficient erythropoietin production due to a reduction of functional renal mass (see Decreased Erythropoiesis). Other causes include deficiencies of iron, folate, and vitamin B_{12}.

Symptoms and Signs

Patients with mildly diminished renal reserve are asymptomatic. Even patients with mild to moderate renal insufficiency may have no symptoms despite elevated BUN and creatinine. Nocturia is often noted, principally due to a failure to concentrate the urine. Lassitude, fatigue, anorexia, and decreased mental acuity often are the earliest manifestations of uremia.

With more severe renal insufficiency (eg, creatinine clearance < 10 mL/min for patients without diabetes and < 15 mL/min for those with diabetes), neuromuscular symptoms may be present, including coarse muscular twitches, peripheral sensory and motor neuropathies, muscle cramps,

hyperreflexia, restless legs syndrome, and seizures (usually the result of hypertensive or metabolic encephalopathy).

Anorexia, nausea, vomiting, weight loss, stomatitis, and an unpleasant taste in the mouth are almost uniformly present. The skin may be yellow-brown. Occasionally, urea from sweat crystallizes on the skin (uremic frost). Pruritus may be especially uncomfortable. Undernutrition leading to generalized tissue wasting is a prominent feature of chronic uremia.

In advanced CKD, pericarditis and GI ulceration and bleeding are common. Hypertension is present in > 80% of patients with advanced CKD, is usually related to hypervolemia, and is occasionally the result of activation of the renin-angiotensin-aldosterone system. Heart failure caused by hypertension or coronary artery disease and renal retention of sodium and water may lead to dependent edema.

Diagnosis

- Electrolytes, BUN, creatinine, phosphate, calcium, CBC, urinalysis (including urinary sediment examination)
- Ultrasonography
- Sometimes renal biopsy

CKD is usually first suspected when serum creatinine rises. The initial step is to determine whether the renal failure is acute, chronic, or acute superimposed on chronic (ie, an acute disease that further compromises renal function in a patient with CKD—see Table: Distinguishing Acute Kidney Injury From Chronic Kidney Disease). The cause of renal failure is also determined. Sometimes determining the duration of renal failure helps determine the cause; sometimes it is easier to determine the cause than the duration, and determining the cause helps determine the duration.

Distinguishing Acute Kidney Injury From Chronic Kidney Disease

Finding	*Comment*
Prior known increase in serum creatinine	Most reliable evidence of CKD
Renal sonogram showing small kidneys	Usually CKD
Renal sonogram showing normal or enlarged kidneys	May be AKI or some forms of CKD (diabetic nephropathy, acute hypertensive nephrosclerosis, PCKD, myeloma, rapidly progressive glomerulonephritis, infiltrative diseases [eg, lymphoma, leukemia, amyloidosis], obstruction)
Oliguria, daily increases in serum creatinine and BUN	Probably AKI or AKI superimposed on CKD
Eye-band keratopathy	Probably CKD
No anemia	Probably AKI or CKD due to PCKD
Severe anemia, hyperphosphatemia, and hypocalcemia	Possibly CKD but may be AKI
Subperiosteal erosions on radiography	Probably CKD
Chronic symptoms or signs (eg, fatigue, nausea, pruritus, nocturia, hypertension)	Usually CKD

AKI = acute kidney injury; CKD = chronic kidney disease; PCKD = polycystic kidney disease.

Testing includes urinalysis with examination of the urinary sediment, electrolytes, urea nitrogen, and creatinine, phosphate, calcium, and CBC. Sometimes specific serologic tests are needed to determine the cause. Distinguishing acute kidney injury from CKD is most helped by a history of an elevated creatinine level or abnormal urinalysis. Urinalysis findings depend on the nature of the underlying disorder, but broad (> 3 WBC diameters wide) or especially waxy (highly refractile) casts often are prominent in advanced renal failure of any cause.

An ultrasound examination of the kidneys is usually helpful in evaluating for obstructive uropathy and in distinguishing acute kidney injury from CKD based on kidney size. Except in certain conditions, patients with CKD have small shrunken kidneys (usually < 10 cm in length) with

thinned, hyperechoic cortex. Obtaining a precise diagnosis becomes increasingly difficult as renal function reaches values close to those of end-stage renal disease. The definitive diagnostic tool is renal biopsy, but it is not recommended when ultrasonography indicates small, fibrotic kidneys.

Classification

Staging CKD is a way of quantifying its severity. CKD has been classified into 5 stages.

- Stage 1: Normal GFR (≥ 90 mL/min/1.73 m^2) plus either persistent albuminuria or known structural or hereditary renal disease
- Stage 2: GFR 60 to 89 mL/min/1.73 m^2
- Stage 3: GFR 30 to 59 mL/min/1.73 m^2
- Stage 4: GFR 15 to 29 mL/min/1.73 m^2
- Stage 5: GFR < 15 mL/min/1.73 m^2

GFR (in mL/min/1.73 m^2) in CKD can be estimated by: $186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203}$. The result is multiplied by 0.742 if the patient is female and by 1.21 if the patient is African American. For female African Americans, the result is multiplied by 0.742 × 1.21 (0.898). This calculation is not very accurate for patients who are older and sedentary, very obese, or very thin. Alternatively, GFR can be estimated using the Cockcroft-Gault equation to approximate creatinine clearance; this equation tends to overestimate GFR by 10 to 40%.

The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula is more accurate than the MDRD and Cockcroft and Gault formulas, particularly for patients with a GFR near normal values. The CKD-EPI equation yields fewer falsely positive results indicating chronic kidney disease and predicts outcome better than the other formulas.

Prognosis

Progression of CKD is predicted in most cases by the degree of proteinuria. Patients with nephrotic-range proteinuria (> 3 g/24 h or urine protein/creatinine > 3) usually have a poorer prognosis and progress to renal failure more rapidly. Progression may occur even if the underlying disorder is not active. In patients with urine protein < 1.5 g/24 h, progression usually occurs more slowly if at all. Hypertension, acidosis, and hyperparathyroidism are associated with more rapid progression as well.

Treatment

- Control of underlying disorders
- Possible restriction of dietary protein, phosphate, and potassium
- Vitamin D supplements
- Treatment of anemia and heart failure
- Doses of all drugs adjusted as needed
- Dialysis for severely decreased GFR, uremic symptoms, or sometimes hyperkalemia or heart failure
- Maintaining sodium bicarbonate level at 23 mmol/L

Underlying disorders and contributory factors must be controlled. In particular, controlling hyperglycemia in patients with diabetic nephropathy and controlling hypertension in all patients substantially slows deterioration of GFR. Recent guidelines suggest a target BP of < 140/90 mm Hg, but some authors continue to recommend about 110 to 130/ < 80 mm Hg. ACE inhibitors and angiotensin II receptor blockers decrease the rate of decline in GFR in patients with most causes of CKD, particularly those with proteinuria. Increasing evidence suggests that, compared with either drug alone, combined use of ACE inhibitors and angiotensin II receptor blockers increases incidence of complications and does not slow decline in renal function, even though combined use does reduce proteinuria more.

Activity need not be restricted, although fatigue and lassitude usually limit a patient's capacity for exercise. Pruritus may respond to phosphate binders if serum phosphate is elevated. If patients do not respond, ultraviolet phototherapy may help.

Nutrition

Severe protein restriction in renal disease is controversial. However, moderate restriction (0.8 g/kg/day) is safe and easy for most patients to tolerate. Some experts recommend 0.6 g/kg/day for

patients with diabetes and, for patients without diabetes, > 0.8 g/kg/day if GFR is 25 to 55 mL/min/1.73 m^2 or 0.6 g/kg/day if GFR is 13 to 24 mL/min/1.73 m^2. Many uremic symptoms markedly lessen when protein catabolism and urea generation are reduced. Sufficient carbohydrate and fat are given to meet energy requirements and prevent ketosis. Patients for whom < 0.8 g/kg/day has been prescribed should be closely followed by a dietician.

Because dietary restrictions may reduce necessary vitamin intake, patients should take a multivitamin containing water-soluble vitamins. Administration of vitamin A and E is unnecessary. Vitamin D in the form of 1,25-dihydroxyvitamin D (calcitriol) or its analogs should be given as indicated by PTH concentrations. Dose is determined by stage of CKD, PTH concentration, and phosphate concentrations. Target levels for calcium are 8.4 to 9.5 mg/dL (2.10 to 2.37 mmol/L); for the calcium-phosphate product, < 55 mg^2/dL^2.

Target Levels for PTH and Phosphate in Chronic Kidney Disease

Chronic Kidney Disease Stage	*PTH (pg/mL)*	*Phosphate (mg/dL [mmol/L])*
3	*35–70*	*2.7–4.6 (0.87–1.49)*
4	*70–110*	*2.7–4.6 (0.87–1.49)*
5	*150–300*	*3.5–5.5 (1.13–1.78)*

PTH = parathyroid hormone.

A typical starting dose is calcitriol (or a calcitriol analog) 0.25 mcg po once/day or 1 to 4 mcg 2 times/wk. PTH levels are not corrected to normal because doing so risks precipitating adynamic bone disease.

Dietary modification may be helpful for hypertriglyceridemia. In patients with hypercholesterolemia, a statin is effective. Fibric acid derivatives (clofibrate, gemfibrozil) may increase risk of rhabdomyolysis in patients with CKD, especially if taken with statin drugs, whereas ezetimibe (which reduces cholesterol absorption) appears relatively safe. Correction of hypercholesterolemia may slow progression of the underlying renal disease and reduce coronary risk.

Fluid and electrolytes

Water intake is restricted only when serum sodium concentration is < 135 mmol/L or there is heart failure or severe edema.

Sodium restriction of 1.5 g/day benefits patients, especially those with edema, heart failure, or hypertension.

Potassium intake is closely related to meat, vegetable, and fruit ingestion and usually does not require adjustment. However, foods (especially salt substitutes) rich in potassium should generally be avoided. Hyperkalemia is infrequent (unless there is hyporeninemic hypoaldosteronism or potassium-sparing diuretic therapy) until end-stage renal failure, when potassium intake may need to be restricted to ≤ 50 mmol/day. Mild hyperkalemia (< 6 mmol/L) can be treated by reducing potassium intake and correcting metabolic acidosis. More severe hyperkalemia (> 6 mmol/L) warrants urgent treatment.

Phosphate restriction to < 1 g/day is often sufficient to maintain phosphate level in the target range during the early phase of stages 3 and 4 CKD. However, in the later phases, phosphate binders, such as calcium salts (acetate or carbonate but avoid citrate) or non–calcium-containing phosphate binders (sevelamer) are often necessary. No more than 1500 mg/day of elemental calcium should be given as binders (2000 mg/day of total calcium; binders plus dietary calcium).

Metabolic acidosis should be treated to bring serum bicarbonate to normal (> 23 mmol/L) and help reverse or slow muscle wasting, bone loss, and progression of CKD. Acidosis can be corrected with oral alkali sources such as sodium bicarbonate or an alkaline-ash diet (primarily fruits and vegetables). Sodium bicarbonate 1 to 2 g po bid is given and amount is increased gradually until bicarbonate concentration is about 23 mmol/L or until evidence of sodium overloading prevents

further therapy. If the alkaline-ash diet is used, serum potassium is monitored because fruits and vegetables contain potassium.

Anemia and coagulation disorders

Anemia is a common complication of moderate to advanced CKD (≥ stage 3), and, when severe, is treated with erythropoiesis-stimulating agents (ESA), such as recombinant human erythropoietin (eg, epoetin alfa). Due to risk of cardiovascular complications, including stroke, thrombosis, and death, the lowest dose of these agents needed to keep the Hb between 10 and 11 g/dL is used. Because of increased iron utilization with stimulated erythropoiesis, iron stores must be replaced, often requiring parenteral iron. Iron concentrations, iron-binding capacity, and ferritin concentrations should be followed closely. Target transferrin saturation (TSAT), calculated by dividing serum iron by total iron binding capacity and multiplying by 100%, should be > 20%, Target ferritin in patients not on dialysis is >100 ng/mL. Transfusion should not be done unless anemia is severe (Hb < 8 g/dL) or causes symptoms.

The bleeding tendency in CKD rarely needs treatment. Cryoprecipitate, RBC transfusions, desmopressin 0.3 to 0.4 mcg/kg (20 mcg maximum) in 20 mL of isotonic saline IV over 20 to 30 min, or conjugated estrogens 2.5 to 5 mg po once/day help when needed. The effects of these treatments last 12 to 48 h, except for conjugated estrogens , which may last for several days.

Heart failure

Symptomatic heart failure is treated with sodium restriction and diuretics. If left ventricular function is depressed, ACE inhibitors and beta-blockers (carvedilol or metoprolol) should be used. Digoxin may be added, but the dosage must be reduced. Diuretics such as furosemide usually are effective even when renal function is markedly reduced, although large doses may be needed.

Moderate or severe hypertension should be treated to avoid its deleterious effects on cardiac and renal function. Patients who do not respond to sodium restriction (1.5 g/day), should receive diuretic therapy (furosemide 80 to 240 mg po bid). Hydrochlorothiazide 12.5 mg (starting dose) to 25 mg (rarely up to 50 mg) po once/day or metolazone 5 to 10 mg po once/day or bid may be added to high-dose furosemide therapy if hypertension or edema is not controlled. Even in renal failure, the combination of a thiazide diuretic with a loop diuretic is quite potent and must be used with caution to avoid overdiuresis.

Occasionally, dialysis may be required to control heart failure. If reduction of the ECF volume does not control BP, conventional antihypertensives are added. Azotemia may increase with such treatment and may be necessary for adequate control of heart failure and/or hypertension.

Drugs

Renal excretion of drugs is often impaired in patients with renal failure. Common drugs that require revised dosing include penicillins, cephalosporins, aminoglycosides, fluoroquinolones, vancomycin, and digoxin. Hemodialysis reduces the serum concentrations of some drugs, which should be supplemented after hemodialysis. It is strongly recommended that physicians consult a reference on drug dosing in renal failure before prescribing drugs to these very vulnerable patients. Some appropriate references include CKD and Drug Dosing: Information for Providers , Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO), and Drug Dosing Adjustments in Patients with Chronic Kidney Disease. Most experts avoid non-steroidal antiinflammatory drugs in patients with CKD because they may worsen renal function,

Certain drugs should be avoided entirely in patients with chronic kidney disease. They include nitrofurantoin, metformin, and phenazopyridine. The MRI contrast agent gadolinium has been associated with the development of nephrogenic systemic fibrosis in some patients; because risk is particularly high if patients have estimated GFR < 30mL/min/1.73m^2, gadolinium should be avoided whenever possible in these patients.

Dialysis

Dialysis is usually initiated at the onset of either of the following:

- Uremic symptoms (eg, anorexia, nausea, vomiting, weight loss, pericarditis, pleuritis)
- Difficulty controlling fluid overload, hyperkalemia, or acidosis

These problems typically occur when the estimated GFR reaches ≤ 10 mL/min in a patient without diabetes or ≤ 15 mL/min in a patient with diabetes; patients whose estimated GFR values are near these values should be closely monitored so that these signs and symptoms are recognized early. Dialysis is best anticipated so that preparations can be made and urgent insertion of a hemodialysis catheter can be avoided. Such preparations usually begin when the patient is in early to mid stage 4 CKD; preparation allows time for patient education, selection of the type of dialysis, and timely creation of an arteriovenous fistula or placement of a peritoneal dialysis catheter.

Hemodialysis (Intermittent Hemodialysis)

In hemodialysis, a patient's blood is pumped into a dialyzer containing 2 fluid compartments configured as bundles of hollow fiber capillary tubes or as parallel, sandwiched sheets of semipermeable membranes. In either configuration, blood in the first compartment is pumped along one side of a semipermeable membrane while a crystalloid solution (dialysate) is pumped along the other side, in a separate compartment, in the opposite direction. Concentration gradients of solute between blood and dialysate lead to desired changes in the patient's serum solutes, such as a reduction in urea nitrogen and creatinine; an increase in HCO_3; and equilibration of Na, Cl, K, and Mg. The dialysate compartment is under negative pressure relative to the blood compartment and has a higher osmolality to prevent filtration of dialysate into the bloodstream and to remove the excess fluid from the patient. The dialyzed blood is then returned to the patient.

The patient is usually systemically anticoagulated during hemodialysis to prevent blood from clotting in the dialysis machine. However, hemodialysis treatment may also be done with regional anticoagulation of the dialysis circuit (using heparin or trisodium citrate) or with saline flush, in which 50 to 100 mL of saline every 15 to 30 min clears the dialysis circuit of any blood clots.

The immediate objectives of hemodialysis are to correct electrolyte and fluid imbalances and remove toxins. Longer term objectives in patients with renal failure are to

- Optimize the patient's functional status, comfort, and BP
- Prevent complications of uremia
- Prolong survival

The optimal "dose" of hemodialysis is uncertain, but most patients do well with 3 to 5 h of hemodialysis 3 times/wk. One way to assess the adequacy of each session is by measuring BUN before and after each session. A ≥ 65% decrease of BUN from predialysis level ([predialysis BUN − postdialysis BUN]/predialysis BUN × 100% is ≥ 65%) indicates an adequate session. Specialists may use other, more calculation-intensive formulas, such as KT/V ≥ 1.2 (where K is the urea clearance of the dialyzer in mL/min, T is dialysis time in minutes, and V is volume of distribution of urea [which is about equal to total body water] in mL). Hemodialysis dose can be increased by increasing time on dialysis, blood flow, membrane surface area, and membrane porosity. Nightly hemodialysis sessions (6 to 8 h, 5 to 6 days/wk) and short (1.5 to 2.5 h) daily sessions, when available, are used selectively for patients who have any of the following:

- *Excessive fluid gain between dialysis sessions*
- *Frequent hypotension during dialysis*
- *Poorly controlled BP*
- *Hyperphosphatemia that is otherwise difficult to control*

These daily sessions are most economically feasible if patients can do hemodialysis at home.

Clinical Calculator:; Lean Body Weight (Female)

Clinical Calculator:; Lean Body Weight (Male)

Vascular access

Hemodialysis is usually done through a surgically created arteriovenous fistula. However, dialysis can be done through a central vein catheter if an arteriovenous fistula has not yet been created or is not ready for use or if creation of an arteriovenous fistula is impossible. The primary disadvantages of central vein catheters are a relatively narrow caliber that does not allow for blood flow high enough to achieve optimal clearance and a high risk of catheter site infection and thrombosis. Central venous catheterization for hemodialysis is best done by using the right internal jugular vein. Most internal jugular vein catheters remain useful for 2 to 6 wk if strict aseptic skin care is practiced

and if the catheter is used only for hemodialysis. Catheters with a subcutaneous tunnel and fabric cuff have a longer life span (50% functional at 1 yr) and may be useful for patients in whom creation of an arteriovenous fistula is impossible.

Surgically created arteriovenous fistulas are better than central ven

ous catheters because they are more durable and less likely to become infected. But they are also prone to complications (thrombosis, infection, aneurysm or pseudoaneurysm). A newly created fistula may take 3 to 6 mo to mature and become usable, so in patients with chronic kidney disease, the fistula is best created at least 6 mo before the anticipated need for dialysis. The surgical procedure anastomoses the radial, brachial, or femoral artery to an adjacent vein in an end-of-the-vein to the side-of-the-artery fashion. When the adjacent vein is not suitable for access creation, a piece of prosthetic graft is used. For patients who have poor veins, an autogenous saphenous vein graft is also an option.

Vascular access complications

Complications such as infection, stenosis, thrombosis (often in a stenotic passage), and pseudoaneurysm or aneurysm, significantly limit the quality of hemodialysis that can be delivered, increase long-term morbidity and mortality, and are common enough that patients and practitioners should be vigilant for suggestive changes. These changes include pain, edema, erythema, breaks in the skin overlying the access, absence of bruit and pulse in the access, hematoma around the access, and prolonged bleeding from the dialysis cannula puncture site. Infection is treated with antibiotics, surgery, or both.

The fistula may be monitored for signs of impending failure by serial Doppler dilution blood flow measurements, thermal or urea dilution techniques, or by measurement of the static venous chamber pressures. One of these tests is usually recommended at least monthly. Treatment of stenosis, thrombosis, pseudoaneurysm, or aneurysm may involve angioplasty, stenting, or surgery.

Dialysis complications

Type	*Hemodialysis*	*Peritoneal Dialysis*
Cardiovascular	Air embolism Angina Arrhythmia Cardiac arrest (rare) Cardiac tamponade Hypotension*	Arrhythmia Hypotension* Pulmonary edema
Infectious	Bacteremia Colonization of temporary central venous catheters Exit-site infection of both tunneled and temporary central venous catheters Endocarditis Meningitis Osteomyelitis Sepsis Vascular access cellulitis or abscess	Catheter exit site infection* Peritonitis*
Mechanical	Obstruction of the arteriovenous fistula due to thrombosis or infection Stenosis or thrombosis of the subclavian vein or superior vena cava due to recurrent use of subclavian and internal	Catheter obstruction by clots, fibrin, omentum, or fibrous encasement Dialysate leakage around the catheter Dissection of fluid into the abdominal wall

	jugular vein catheters	Hematoma in the pericatheter tract Perforation of a viscus by the catheter
Metabolic	Hypoglycemia in diabetics who use insulin Hypokalemia Hyponatremia or hypernatremia Iron loss	Hypoalbuminemia Hyperglycemia Hyperlipidemia Obesity
Pulmonary	Dyspnea due to anaphylactic reaction to hemodialysis membrane Hypoxia when acetate buffered dialysate is used	Atelectasis Pleural effusion Pneumonia
Miscellaneous	Amyloid deposits Catheter-related hemorrhage Fever due to bacteremia, pyrogens, or overheated dialysate Hemorrhage (GI, intracranial, retroperitoneal, intraocular) Insomnia Muscle cramps* Pruritus Restlessness Seizures	Abdominal and inguinal hernias Catheter-related intra-abdominal bleeding Hypothermia Peritoneal sclerosis Seizures

*Most common complications overall.

Hypotension is most common and has multiple causes, including too-rapid water removal, osmotic fluid shifts across cell membranes, acetate in the dialysate, heat-related vasodilation, allergic reactions, sepsis, and underlying conditions (eg, autonomic neuropathy, cardiomyopathy with poor ejection fraction, myocardial ischemia, arrhythmias).

Many patients also have restless leg syndrome, cramps, pruritus, nausea and vomiting, headache, and chest and back pain. In most cases, these complications occur for unknown reasons, but some may be part of a first-use syndrome (when the patient's blood is exposed to cuprophane or cellulose membranes in the dialyzer) or dialysis dysequilibrium syndrome, a syndrome thought to be caused by too rapid removal of urea and other osmolytes from the serum, causing osmotic movement of fluid into the brain. More severe cases of dialysis dysequilibrium manifest as disorientation, restlessness, blurred vision, confusion, seizures, and even death.

Dialysis-related amyloidosis affects patients who have been on hemodialysis for years and manifests as carpal tunnel syndrome, bone cysts, arthritis, and cervical spondyloarthropathy. Dialysis-related amyloidosis is believed to be less common with the high-flux dialyzers in wide use today because $ß_2$-microglobulin (the protein causing the amyloidosis) is removed more effectively with these dialyzers.

Transplantation

If a living kidney donor is available, better long-term outcomes occur when a patient receives the transplanted kidney early, even before beginning dialysis. Patients who are transplant candidates but have no living donor should receive a cadaveric kidney transplant as early after initiating dialysis as possible.

Equipment: class room, 6-channel ECG machine CARDIOLINE 100 L and Cardioline 200 + II S, ultrasound system Mylab Six CristaLine with 3 detectors.

Lesson time: 4 hours

Plan

I. Organization moments (Greeting, head count, theme announce, aim of lesson, motivating applicants to study the topic).
II. Control of basic knowledges (The task source for self-knowledge skills tests from «KROK2» - additional materials, cheking workbooks

II.1 Requirements for theoretical readiness of applicants to perform practical classes.

Requirements to knowledges:
- Definition of chronic kidney disease
- Modern aspects of etiology and pathophysiology of chronic kidney disease
- Classification of chronic kidney disease
- Clinical manifestation of chronic kidney disease
- Laboratory and instrumental investigation of chronic kidney disease
- Carry out differential diagnosis of chronic kidney disease
- Complications of chronic kidney disease
- Treatment, rehabilitation of patients with chronic kidney disease
- Prognosis and disability of patients with chronic kidney disease

list of didactic units
- To get a detailed anamnesis
- To do physical examination of patient, to diagnose and to estimate changes in condition
- To make a plan of additional investigation and estimate it
- Justify and make a preliminary and clinical diagnoses of chronic kidney disease
- Basic principles of treatment chronic kidney disease
- Estimation of exacerbation of chronic kidney disease and its treatment
- Estimation of clinical examination, CBC, blood tests, urinalysis, Nechiporenko`s test, Zimnitsky`s test, kidney ultrasound.

II.2 Questions (MSQ, clinical cases) for basic knowledge examination of topic

1. Patient 48 years. Complaints: loss of appetite, general weakness, increased blood pressure to 180/110 mmHg. Considers himself ill for 5 years when revealed increasing of serum creatinine. Objectively - satisfactory condition. Laboratory tests: a general analysis of urine protein 0.5 g / l, RBC 15-20 in f/v, WBC 3-4 in f/v., gravity 1005; biochemical tests: protein 65 g/l, creatinine 435 mcmol/l, urea 15,5 mmol/l, cholesterol 5,1 mmol/l. What the diagnosis is more likely?
A. Acute glomerulonephritis
B. Chronic glomerulonephritis
C. Chronic renal falure +
D. Amyloidosis
E. Pyelonephritis
2. Patient 58 years. Complaints: loss of appetite, general weakness, increased blood pressure to 180/110 mmHg. Considers himself ill for 5 years when revealed increasing of serum creatinine. Objectively - satisfactory condition. Laboratory tests: a general analysis of urine protein 0.5 g / l, RBC 15-20 in f/v, WBC 3-4 in f/v., gravity 1005; biochemical tests: protein 65 g/l, creatinine 435 mcmol/l, urea 15,5 mmol/l, cholesterol 5,1 mmol/l. Which of drug is contrindicated?
A. Enalapril +
B. Metoprolol
C. Amlodipine
D. Ferrolek

E. Vitamin B12

3. Patient 54 years. Admitted to the Cardiology Department due to suspected myocardial infarction. From history we know that within 3 years of age treated with hemodialysis. Which of the following medications is contraindicated ?

A. Enalapril

B. Metaprolol

C. Potassium aspartat +

D. Hitroglycerin

E. Candesartan

4. Patient 45 years. Complaints: general weakness, loss of appetite, nausea. In the history - surgical interventions due to calculous cholecystitis, appendectomy. Objective - a state of moderate severity, pale skin, no swelling. BP 150/100 mm Hg, HR 60 bpm. Laboratory tests: a general analysis of urine protein 0.25 g / l, RBC 15-20 in f/v, WBC 3-4 in f/v., gravity 1001; biochemical tests: protein 68 g/l, creatinine 735 mcmol/l, urea 25,5 mmol/l, potassium 6.4, cholesterol 5,1 mmol/l, hemoglobine 72 g/l. Which of the following is a contraindication to treatment by peritoneal dialysis ?

A. Creatinine 735 mcmol/l

B. Anemia

C. Hyperpotassiumemia

D. Surgical interventions in anamnesis +

E. Age

5. Patient 28 years. Diabetes mellitus since 7 years old. Complaints about loss of appetite, general weakness, increased blood pressure to 150/110 mmHg. Increases in serum creatinine was revealed 3 years ago. Laboratory tests: a general analysis of urine protein 1.5 g / l, RBC 5-7 in f/v, WBC 15-25 in f/v., gravity 1005; biochemical tests: protein 75 g/l, creatinine 335 mcmol/l, urea 15,5 mmol/l, cholesterol 5,1 mmol/l, glucose 7,5 mmol/l, hemoglobine 92 g/l. What drug is less effective?

A. Enalapril

B. Metaprolol

C. Potassium apartat +

D. Hitroglycerin

E. Candesartan

6. Patient 38 years. Complaints about loss of appetite, general weakness, increased blood pressure to 160/100 mmHg. Increases in serum creatinine was revealed 3 years ago. Laboratory tests: a general analysis of urine protein 1.5 g / l, RBC 5-7 in f/v, WBC 15-25 in f/v., gravity 1005; biochemical tests: protein 75 g/l, creatinine 255 mcmol/l, urea 11,5 mmol/l, cholesterol 5,1 mmol/l, glucose 4,5 mmol/l, hemoglobine 122 g/l. What drug is most effective?

A. Enalapril +

B. Metaprolol

C. Potassium apartat

D. Hitroglycerin

E. Candesartan

7. Patient 42 years. Admitted to the Cardiology Department due to suspected myocardial infarction. Complaints: general weakness, palpitation. From history we know that within 3 years of age treated with hemodialysis. Objective: grave condition, clear consciousness, BP 140/90 mm Hg, HR 42 bpm. What changes do you expect to find in the study of blood electrolytes?

A. Hypersodiumemia

B. Hypercalciumemia

C. Hyperpotassiumemia +

D. Hyperglycemia

E. Hypocalciumemia

8. Patient 42 years. Within 2 years of age treated with hemodialysis. Which of the following products is prohibited?

A. Meat +
B. Fish
C. Fried potatoes
D. Beets
E. Cheese

9. Male 47 years old. Complaints of general weakness, nausea, reducing the number of urine. The complaints appeared a day after working with paint. Objective - a state of moderate severity, normal skin, swelling of ankles. BP 150/100 mm Hg, HR 78 bpm. Laboratory tests: a general analysis of urine protein 0.25 g / l, RBC 15-20 in f/v, WBC 3-4 in f/v., gravity 1001; biochemical tests: protein 68 g/l, creatinine 215 mcmol/l, urea 12,5 mmol/l, potassium 4,4, cholesterol 5,1 mmol/l, hemoglobine 132 g/l. What the diagnosis is more likely?

A. Acute glomerulonephritis +
B. Chronic glomerulonephritis
C. Chronic renal falure
D. Amyloidosis
E. Pyelonephritis

10. Patient 48 years. Chronic glomerulonephritis for 10 years. Complaints: loss of appetite, general weakness, increased blood pressure to 150/110 mmHg. Increases in serum creatinine was revealed 3 years ago. Laboratory tests: a general analysis of urine protein 2,1 g / l, RBC 5-7 in f/v, WBC 15-25 in f/v., gravity 1015; biochemical tests: protein 55 g/l, creatinine 435 mcmol/l, urea 15,5 mmol/l, cholesterol 5,1 mmol/l, glucose 4,5 mmol/l, hemoglobine 92 g/l. What drug is contrindicated?

A. Furosemide
B. Etacrine acid
C. Spironolacton +
D. Torasemide

III. Proffesional skills formation (skills of patient`s management, treatment)

Professional algorithms: work with a patient (according to patients-students conversation algorithm).

During examination students must use next algorithm:

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Collecting data on patient complains, medical history, life history
5. Interpretation of clinical, laboratory and instrumental studies
6. Explanation for patient of next acting (hospitalization, workup)
7. End of conversation

Physical examination of patient with internal diseases

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Explanation of investigations are needed, taking agreement
5. Telling about possible negative feelings during investigation
6. Preparing to examination (clean warm hands, accurate nails, warm phonendoscope, screen if needed)
7. Examination (demonstration of clinical skills)
8. Interpretation of clinical, laboratory and instrumental studies
9. End of conversation

Telling to patient with internal diseases investigation results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect

4. Correct and understandable for patient explanation of investigation results
5. Conversation with patient (comparing new and previous examination results, check if explanation is clear)
6. End of conversation

Planning and prognosing treatment results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of treatment
5. Conversation with patient (explanation of features taking pills, duration of taking drugs, possible side effects) Check if explanation is clear
6. End of conversation

Telling treatment prognosis

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of expected treatment results
5. Conversation with patient (explanation of importance of life-long treatment, taking medications according to list, check if explanation is clear)
6. End of conversation

Task 1

1. Collect complains, anamnesis, examination of patients with chronic kidney disease
2. Identify clinical and instrumental symptoms
3. Make a syndrome based on symptoms and lab. tests
4. Identify the leading clinical syndrome
5. Assign laboratory and instrumental examination (CBC, urine analysis, blood tests, Nechiporenko`s test, Zimnitsky`s test, kidney ultrasound)
6. Carry out differential diagnosis acute kidney injury with chronic kidney disease
7. Make a clinical diagnosis
8. Determine a degree of disability

Task 2

Prescribing different variants of treatment according to guidelines

Task 3

Work in Internet, work with thematic literature in department library room.
Student must fill patient examination protocol (example is added).

Control materials for final part of the lesson:

The cases for self-control with standard answers.

1. A 24 y.o. patient complains of nausea, vomiting, headache, shortness of breath. He had an acute nephritis being 10 y.o. Proteinuria was found out in urine. Objectively: a skin is grey-pale, the edema is not present. Accent of II tone above aorta. BP 140/100-180/100 mm Hg. Blood level of residual N_2- 6,6 mmol/L, creatinine- 406 mmol/L. Day's diuresis- 2300 ml, nocturia. Specific density of urine is 1009, albumin- 0,9 g/L, WBC- 0-2 in f/vis. RBC.- single in f/vis., hyaline casts single in specimen. Your diagnosis?

A Chronic nephritis with violation of kidney function
B Feochromocitoma
C Hypertensive illness of the II degree
D Nephrotic syndrome
E Stenosis of kidney artery

2. A 37-year-old patient was brought to resuscitation unit. General condition of the patient is very serious. Sopor. The skin is grey, moist. Turgor is decreased. Pulse is rapid, intense. BP - 160/110 mm Hg, muscle tonus is increased. Hyperreflexia. There is an ammonia odor in the air. What is the presumptive diagnosis?
A Uraemic coma
B Alcoholic coma
C Hyperglycemic coma
D Hypoglycemic coma
E Cerebral coma
3. A 28-year-old woman has a 12-year history of chronic glomerulonephritis with latent course. Over the past six months she has developed general weakness, loss of appetite, low work performance, nausea. The patient complains of headache, pain in the joints. On examination: anemia, blood urea - 34,5 millimole/l, blood creatinine - 0,766 millimole/l, hyperkalemia. What complication has developed?
A Acute renal insufficiency
B Chronic renal insufficiency
C Nephrotic syndrome
D Renal amyloidosis
E Pyelonephritis
4. A 30-year-old woman with a long history of chronic pyelonephritis complains about considerable weakness, sleepiness, decrease in diuresis down to 100 ml per day. AP- 200/120 mm Hg. In blood: creatinine - 0,62 millimole/l, hypoproteinemia, albumines - 32 g/l, potassium - 6,8 millimole/l, hypochromic anemia, increased ESR. What is the first step in the patient treatment tactics?
A Blood transfusion
B Antibacterial therapy
C Enterosorption
D Haemosorption
E Haemodialysis
5. A 35 year old patient who suffers from chronic glomerulonephritis and has been hemodialysis-dependent for the last three years developed intermissions of heart activity, hypotension, progressing weakness, dyspnea. ECG showed bradycardia, atrioventricular block type I, high pointed waves T. The day before the flagrant violation of diet took place. What is the most probable cause of these changes?
A Hyperkaliemia
B Hyperhydratation
C Hypokaliemia
D Hypernatriemia
E Hypocalciemia
6. 56-yr-old female, who suffered from diabetes mellitus for 15 years, presents to your office with breathlessness, vomiting, facial edema, fatigue. In the laboratory investigation: Hb-76 g/l, blood urine nitrates – 52 mmol/l, serum creatinine – 978 μmol/l, potassium (K+) – 6,2 mmol/l. Urine analyses: proteinuria – 1,65 g/l. Chronic kidney disease (CKD) was diagnosed. The stage of CKD in the patient should be estimated by level of:
A. Serum ctreatinine
B. Glomerular filtration rate
C. Blood urine nitrates
D. Blood hemoglobin
E. Protein in urine
7. A 39-year-old patient complains of morning headache, appetite loss, nausea, morning vomi-ting, periodic nasal haemorrhages. The patient had acute glomerulonephritis at the age of 15. Examination revealed rise of arterial pressure up to 220/130 mm Hg, skin haemorrhages on his arms and legs, pallor of skin and mucous membranes. What biochemical parameter is the most important

for making diagnosis in this case?

A. Blood bilirubin
B. Blood sodium
C. Blood creatinine
D. Uric acid
E. Fibrinogen

8. A 58-year-old female patient complains about periodical headache, dizziness and ear noise. She has been suffering from diabetes mellitus for 15 years. Objectively: heart sounds are rhythmic, heart rate is 76/min, there is diastolic shock above aorta, AP is 180/110 mm Hg. In urine: OD- 1,014. Daily loss of protein with urine is 1,5 g. What drug should be chosen for treatment of arterial hypertension?

A. Thiazide diuretic
B. α-blocker
C. Calcium channel antagonist
D. β-blocker
E. Ihibitor of angiotensin converting enzyme

9. A patient 65 years old was admitted with complaints of severe weakness, drowsiness, decrease daily urine output till 300 ml, shortness of breath on exertion, dizziness, nausea, palpitations, loss of appetite, edema of the face and lower extremities. Over 9 years is suffering from diabetes. Since 20 y.o. peptic ulcer of the duodenum, at present time - in remission. In blood: glucose - 11.3 mmol/l, creatinine 142 mcmol/l, hemoglobin - 82 g/l. Daily protein excretion - 3,9 g. Select a drug for anemia treatment.

A. Recormon
B. Ferrum-Lek
C. Cyanocobalamine
D. Folic acid
E. Red Blood Cells transfusion

10. 42 years old patient is suffering from chronic glomerulonephritis for 15 years. Objectively: BP - 150 mmHg, heart rate - 84 bpm, edema of the face, legs and feet. Blood test: total protein - 56 g/l, creatinine - 132 mcmol/l, GFR - 66,8 ml/min. Urine test: protein - 1,98 g/l, WBC - 12-16, RBC leached - 8-14, hyaline cylinders - 2-4 in f/v. The daily protein excretion - 3,7 g. Diagnosis?

A. CKD III st: glomerulonephritis with nephrotic syndrome
B. CKD II st: glomerulonephritis with nephrotic and urinary syndrome
C. CKD IV st: glomerulonephritis with nephrotic and urinary syndrome
D. CKD I st: glomerulonephritis with urinary syndrome
E. CKD II st: glomerulonephritis with urinary syndrome

Standard answers: 1-E, 2-A, 3-B, 4-E, 5-A, 6-B, 7-C, 8-E, 9-A, 10-B

IV. Making conclusions, telling final marks, tasks for the next lesson

Literature list

- Basic literature source:

1. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention and Treatment of Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD). kdigo.org/wp.../2017-KDIGO-CKD-MBD-GL-Update.pdf

2. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases // Kidney inter. – 2021. – Vol. 100, issue 4. Suppl. P.1-276. doi: 10.1016/j.kint.2021.05.021.

3. Harrison's Principles of Internal Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 3528 p.

4. BMJ Best Practice. Chronic kidney disease. - BMJ publishing group LTD, 2018. – 63 p.

- Additional literature source:

1. Drüeke, Tilman B. “Hyperparathyroidism in Chronic Kidney Disease.” Endotext, edited by Kenneth R Feingold et. al., MDText.com, Inc., 18 October 2021.task

An example of the initial examination of the patient

Passport part: Name, European female of 63 years old.
Complaints: face puffiness, high blood pressure, swelling of the ankles, sometimes nausea, weakness
Medical history: Signs a worsening of the condition about 2 years, when appear
weakness and from time to time face puffiness, a few weeks ago she observe high blood pressure, swelling of the ankles. After a visit to the family doctor began to take torasemide and valsartan, noted a slight improvement in the condition. 1 week ago nausea began to bother her. Turned to a family doctor for help, was sent to the clinic of the medical university. Hospitalization in the internal medicine department with intensive care beds has been agreed.
Life history: Material and living conditions are satisfactory. Tuberculosis, venereal disease denies. No any allergic reaction to the medications. There were no occupational hazards. Hereditary history: father and brother have polycystic kidney disease. Does not smoke, does not abuse alcohol. Gynecological history: there were no pregnancies, no births. She has not been in contact with infectious patients in the last 3 days. She has not left the country for the last 3 years.
Objective status: The general condition of the patient is of moderate severity,
clear consciousness. The physique is correct. The position in bed is active.
The skin and visible mucous membranes are clear, pale. Subcutaneous fat is
developed evenly, with some excess in the abdomen. Nutrition normal. Body mass index = 25 kg/m2. Breathing over the lungs is vesicular, no wheezing. Percussion - clear pulmonary sound. Breath rate - 17 / min. BP –150/80 mm Hg symmetrical on both hands. Heart rhythm is regular, heart rate – 80 beats. in 1 min. Heart sounds are clear. Tongue moist, coated with white bloom. The abdomen is soft and painless on palpation. The liver and spleen are not palpable. The symptom of tapping on the lumbar region is positive on both side. Peripheral edema of feet and ankles, puffy face.
Diagnosis:
Polycystic kidney disease. Chronic kidney disease grade 3a? Secondary anemia?
Examination plan:
1. Cell blood count,
2. blood biochemistry: creatinine, urea, albumin, potassium, ferum, erythropoietin
3. coagulation test,
4. liver function tests,
5. lipid profile
6. urinalysis, Nechiporenko`s test;
7. ECG
8. Kidney ultrasound

Treatment plan:
1. Bed rest, restriction of salt and protein
2. Torasemide 20 mg orally once a day in the morning
3. Valsartan 80 mg orally once a day in the morning
4. Lactulose 30 ml orally three times per day
5. Xerogel polymethylsiloxane 1 capsule orally three times per day
6. Erythropoietin 2000 IU subcutaneously orally three times per week

Practical lesson № 19

Topic 11: Acute kidney injury

Object: To teach students to master the method of examination of patients with respiratory diseases with the selection of the main pulmonological syndromes. To study probable etiological factors, pathogenesis of chronic obstructive pulmonary diseases, their main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis and efficiency of patients.

Basic concepts:

№	Term	Definition
1	Glomerular filtration rate (GFR)	the volume of fluid filtered from the renal (kidney) glomerular capillaries into the Bowman's capsule per unit time.
2	Oliguria	the low output of urine specifically more than 50 ml/day but less than 500ml/day.
3	Anuria	nonpassage of urine or passage of less than 50 milliliters of urine in a day.
4	Dialysis	procedure to remove waste products and excess fluid from the blood when the kidneys stop working properly.
5	Hyperkalemia	an elevated level of potassium (K+) in the blood with levels above 5.5 mmol/l Hyperkalemia can cause an abnormal heart rhythm which can result in cardiac arrest and death.
6	Erythropoietin	a glycoprotein cytokine secreted mainly by the kidney in response to cellular hypoxia; it stimulates red blood cell production (erythropoiesis) in the bone marrow.

Acute kidney injury is a rapid decrease in renal function over days to weeks, causing an accumulation of nitrogenous products in the blood (azotemia). It often results from severe trauma, illness, or surgery but is sometimes caused by a rapidly progressive, intrinsic renal disease. Symptoms include anorexia, nausea, and vomiting. Seizures and coma may occur if the condition is untreated. Fluid, electrolyte, and acid-base disorders develop quickly. Diagnosis is based on laboratory tests of renal function, including serum creatinine. Urinary indices, urinary sediment examination, and often imaging and other tests are needed to determine the cause. Treatment is directed at the cause but also includes fluid and electrolyte management and sometimes dialysis.

In all cases of acute kidney injury (AKI), creatinine and urea build up in the blood over several days, and fluid and electrolyte disorders develop. The most serious of these disorders are hyperkalemia and fluid overload (possibly causing pulmonary edema). Phosphate retention leads to hyperphosphatemia. Hypocalcemia is thought to occur because the impaired kidney no longer produces calcitriol and because hyperphosphatemia causes Ca phosphate precipitation in the tissues. Acidosis develops because hydrogen ions cannot be excreted. With significant uremia, coagulation may be impaired, and pericarditis may develop. Urine output varies with the type and cause of AKI.

Etiology

Causes of AKI can be classified as:
Prerenal
Renal
Postrenal

Prerenal azotemia is due to inadequate renal perfusion. The main causes are ECF volume depletion and cardiovascular disease. Prerenal conditions cause about 50 to 80% of AKI but do not cause permanent kidney damage (and hence are potentially reversible) unless hypoperfusion is severe enough to cause tubular ischemia. Hypoperfusion of an otherwise functioning kidney leads to enhanced reabsorption of Na and water, resulting in oliguria with high urine osmolality and low urine Na.

Renal causes of AKI involve intrinsic kidney disease or damage. Renal causes are responsible for about 10 to 40% of cases. Overall, the most common causes are prolonged renal ischemia and nephrotoxins (including IV use of iodinated radiopaque contrast agents—see Contrast Nephropathy). Disorders may involve the glomeruli, tubules, or interstitium. Glomerular disease reduces GFR and increases glomerular capillary permeability to proteins; it may be inflammatory (glomerulonephritis) or the result of vascular damage from ischemia or vasculitis. Tubules also may be damaged by ischemia and may become obstructed by cellular debris, protein or crystal deposition, and cellular or interstitial edema. Tubular damage impairs reabsorption of Na, so urinary Na tends to be elevated, which is helpful diagnostically. Interstitial inflammation (nephritis) usually involves an immunologic or allergic phenomenon. These mechanisms of tubular damage are complex and interdependent, rendering the previously popular term acute tubular necrosis an inadequate description.

Postrenal azotemia (obstructive nephropathy) is due to various types of obstruction in the voiding and collecting parts of the urinary system and is responsible for about 5 to 10% of cases. Obstruction can also occur within the tubules when crystalline or proteinaceous material precipitates. This form of renal failure is often grouped with postrenal failure because the mechanism is obstructive. Obstructed ultrafiltrate flow in tubules or more distally increases pressure in the urinary space of the glomerulus, reducing GFR. Obstruction also affects renal blood flow, initially increasing the flow and pressure in the glomerular capillary by reducing afferent arteriolar resistance. However, within 3 to 4 h, the renal blood flow is reduced, and by 24 h, it has fallen to < 50% of normal because of increased resistance of renal vasculature. Renovascular resistance may take up to a week to return to normal after relief of a 24-h obstruction. To produce significant azotemia, obstruction at the level of the ureter requires involvement of both ureters unless the patient has only a single functioning kidney. Bladder outlet obstruction is probably the most common cause of sudden, and often total, cessation of urinary output in men.

Urine output: Prerenal causes typically manifest with oliguria, not anuria. Anuria usually occurs only in obstructive uropathy or, less commonly, in bilateral renal artery occlusion, acute cortical necrosis, or rapidly progressive glomerulonephritis.

A relatively preserved urine output of 1 to 2.4 L/day is initially present in most renal causes. In acute tubular injury, output may have 3 phases.

The prodromal phase, with usually normal urine output, varies in duration depending on causative factors (eg, the amount of toxin ingested, the duration and severity of hypotension).

The oliguric phase, with output typically between 50 and 400 mL/day, lasts an average of 10 to 14 days but varies from 1 day to 8 wk. However, many patients are never oliguric. Nonoliguric patients have lower mortality and morbidity and less need for dialysis.

In the postoliguric phase, urine output gradually returns to normal, but serum creatinine and urea levels may not fall for several more days. Tubular dysfunction may persist and is manifested by Na wasting, polyuria (possibly massive) unresponsive to vasopressin, or hyperchloremic metabolic acidosis.

Symptoms and Signs

Initially, weight gain and peripheral edema may be the only findings. Often, predominant symptoms are those of the underlying illness or those caused by the surgical complication that precipitated renal deterioration. Later, as nitrogenous products accumulate, symptoms of uremia may develop, including anorexia, nausea, vomiting, weakness, myoclonic jerks, seizures, confusion, and coma; asterixis and hyperreflexia may be present on examination. Chest pain (typically worse with inspiration or when recumbent), a pericardial friction rub, and findings of pericardial tamponade may occur if uremic pericarditis is present. Fluid accumulation in the lungs may cause dyspnea and crackles on auscultation.

Other findings depend on the cause. Urine may be cola-colored in glomerulonephritis or myoglobinuria. A palpable bladder may be present with outlet obstruction. The costovertebral angle may be tender if the kidney is acutely enlarged.

Diagnosis
Serum creatinine
Urinary sediment
Urinary diagnostic indices
Postvoid residual bladder volume if postrenal cause suspected

AKI is suspected when urine output falls or serum BUN and creatinine rise. Evaluation should determine the presence and type of AKI and seek a cause. Blood tests generally include CBC, BUN, creatinine, and electrolytes (including Ca and phosphate). Urine tests include Na and creatinine concentration and microscopic analysis of sediment. Early detection and treatment increase the chances of reversing renal failure and in some cases preventing it.

A progressive daily rise in serum creatinine is diagnostic of AKI. Serum creatinine can increase by as much as 2 mg/dL/day (180 μmol/L/day), depending on the amount of creatinine produced (which varies with lean body mass) and total body water. A rise of > 2 mg/dL/day suggests overproduction due to rhabdomyolysis.

Urea nitrogen may increase by 10 to 20 mg/dL/day (3.6 to 7.1 mmol urea/L/day), but BUN may be misleading because it is frequently elevated in response to increased protein catabolism resulting from surgery, trauma, corticosteroids, burns, transfusion reactions, parenteral nutrition or GI or internal bleeding.

When creatinine is rising, 24-h urine collection for creatinine clearance and the various formulas used to calculate creatinine clearance from serum creatinine are inaccurate and should not be used in estimating GFR, because the rise in serum creatinine concentration is a delayed function of GFR decline.

Other laboratory findings are progressive acidosis, hyperkalemia, hyponatremia, and anemia. Acidosis is ordinarily moderate, with a plasma HCO3 content of 15 to 20 mmol/L. Serum K concentration increases slowly, but when catabolism is markedly accelerated, it may rise by 1 to 2 mmol/L/day. Hyponatremia usually is moderate (serum Na, 125 to 135 mmol/L) and correlates with a surplus of water. Normochromic-normocytic anemia with an Hct of 25 to 30% is typical.

Hypocalcemia is common and may be profound in patients with myoglobinuric AKI, apparently because of the combined effects of Ca deposition in necrotic muscle, reduced calcitriol production, resistance of bone to parathyroid hormone (PTH), and hyperphosphatemia. During

recovery from AKI, hypercalcemia may supervene as renal calcitriol production increases, the bone becomes responsive to PTH, and Ca deposits are mobilized from damaged tissue.

Determination of cause: Immediately reversible prerenal or postrenal causes must be excluded first. ECF volume depletion and obstruction are considered in all patients. The drug history must be accurately reviewed and all potentially renal toxic drugs stopped. Urinary diagnostic indices (see see Urinary Diagnostic Indices in Prerenal Azotemia and Acute Tubular Injury) are helpful in distinguishing prerenal azotemia from acute tubular injury, which are the most common causes of AKI in hospitalized patients.

Prerenal causes are often apparent clinically. If so, correction of an underlying hemodynamic abnormality should be attempted. For example, in hypovolemia, volume infusion can be tried, in heart failure, diuretics and afterload reducing drugs can be tried, and in liver failure, octreotide can be tried. Abatement of AKI confirms a prerenal cause.

Postrenal causes should be sought in most cases of AKI. Immediately after the patient voids, bedside ultrasonography of the bladder is done (or, alternatively, a urinary catheter is placed) to determine the residual urine in the bladder. A postvoid residual urine volume > 200 mL suggests bladder outlet obstruction, although detrusor muscle weakness and neurogenic bladder may also cause residual volume of this amount. The catheter may be kept in for the first day to monitor hourly output but is removed once oliguria is confirmed (if bladder outlet obstruction is not present) to decrease risk of infection. Renal ultrasonography is then done to diagnose more proximal obstruction. However, sensitivity for obstruction is only 80 to 85% when ultrasonography is used because the collecting system is not always dilated, especially when the condition is acute, an intrarenal pelvis is present, the ureter is encased (eg, in retroperitoneal fibrosis or neoplasm), or the patient has concomitant hypovolemia. If obstruction is strongly suspected, noncontrast CT can establish the site of obstruction and guide therapy.

The urinary sediment may provide etiologic clues. A normal urine sediment occurs in prerenal azotemia and sometimes in obstructive uropathy. With renal tubular injury, the sediment characteristically contains tubular cells, tubular cell casts, and many granular casts (often with brown pigmentation). Urinary eosinophils suggest allergic tubulointerstitial nephritis. RBC casts indicate glomerulonephritis or vasculitis.

Renal causes are sometimes suggested by clinical findings. Patients with glomerulonephritis (see Glomerular Disorders) often have edema, marked proteinuria (nephrotic syndrome), or signs of arteritis in the skin and retina, often without a history of intrinsic renal disease. Hemoptysis suggests granulomatosis with polyangiitis (formerly Wegener granulomatosis) or Goodpasture syndrome. Certain rashes (eg, erythema nodosum, cutaneous vasculitis, discoid lupus) suggest polyarteritis, cryoglobulinemia, SLE, or Henoch-Schönlein purpura. Tubulointerstitial nephritis and drug allergy are suggested by a history of drug ingestion and a maculopapular or purpuric rash.

To further differentiate renal causes, antistreptolysin-O and complement titers, antinuclear antibodies, and antineutrophil cytoplasmic antibodies are determined. Renal biopsy may be done if the diagnosis remains elusive.

Imaging: In addition to renal ultrasonography, other imaging tests are occasionally of use. In evaluating for ureteral obstruction, noncontrast CT is preferred over antegrade and retrograde urography. In addition to its ability to delineate soft-tissue structures and Ca-containing calculi, CT can detect nonradiopaque calculi.

Contrast agents should be avoided if possible. However, renal arteriography or venography may sometimes be indicated if vascular causes are suggested clinically. Magnetic resonance angiography was increasingly being used for diagnosing renal artery stenosis as well as thrombosis of both arteries and veins because MRI used gadolinium, which was thought to be safer than the iodinated contrast agents used in angiography and contrast-enhanced CT. However, recent evidence suggests that gadolinium may be involved in the pathogenesis of nephrogenic systemic fibrosis, a serious complication that occurs only in patients with AKI. Thus, gadolinium should be avoided if possible in patients with renal failure.

Kidney size, as determined with imaging tests, is helpful to know, because a normal or enlarged kidney favors reversibility, whereas a small kidney suggests chronic renal insufficiency.

Prognosis

Although many causes are reversible if diagnosed and treated early, the overall survival rate remains about 50% because many patients with AKI have significant underlying disorders (eg, sepsis, respiratory failure). Death is usually the result of these disorders rather than AKI itself. Most survivors have adequate kidney function. About 10% require dialysis or transplantation—half right away and the others as renal function slowly deteriorates.

Treatment

Immediate treatment of pulmonary edema and hyperkalemia

Dialysis as needed to control hyperkalemia, pulmonary edema, metabolic acidosis, and uremic symptoms

Adjustment of drug regimen

Usually restriction of water, Na, phosphate, and K intake, but provision of adequate protein

Possibly phosphate binders and Na polystyrene sulfonate

Emergency treatment: Life-threatening complications are addressed, preferably in a critical care unit. Pulmonary edema is treated with O2, IV vasodilators (eg, nitroglycerin), and diuretics (often ineffective in AKI). Hyperkalemia is treated as needed with IV infusion of 10 mL of 10% Ca gluconate, 50 g of dextrose, and 5 to 10 units of insulin. These drugs do
not reduce total body K, so further (but slower acting) treatment with 30 g of oral or rectal Na polystyrene sulfonate is begun. Although correction of an anion gap metabolic acidosis with $NaHCO_3$ is controversial, correction of the nonanion gap portion of severe metabolic acidosis (pH < 7.20) is less controversial. The nonanion gap portion may be treated with IV $NaHCO_3$ in the form of a slow infusion (≤ 150 mEq $NaHCO_3$ in 1 L of 5% D/W at a rate of 50 to 100 mL/h). The nonanion gap portion of metabolic acidosis is determined by calculating the increase in anion gap above normal and then subtracting this number from the decrease in HCO_3 from 24 mmol/L. HCO_3 is given to raise the serum HCO_3 by this difference. Because variations in body buffer systems and the rate of acid production are hard to predict, calculating the amount of HCO_3 needed to achieve a full correction is usually not recommended. Instead, HCO_3 is given via continuous infusion and the anion gap is monitored serially.

Hemodialysis or hemofiltration is initiated when:

- severe electrolyte abnormalities cannot otherwise be controlled (eg, K > 6 mmol/L)
- Pulmonary edema persists despite drug treatment
- Metabolic acidosis is unresponsive to treatment
- Uremic symptoms occur (eg, vomiting thought to be due to uremia, asterixis, encephalopathy, pericarditis, seizures)

BUN and creatinine levels are probably not the best guides for initiating dialysis in AKI. In asymptomatic patients who are not seriously ill, particularly those in whom return of renal function is considered likely, dialysis can be deferred until symptoms occur, thus avoiding placement of a central venous catheter with its attendant complications.

General measures: Nephrotoxic drugs are stopped, and all drugs excreted by the kidneys (eg, digoxin, some antibiotics) are adjusted; serum levels are useful.

Daily water intake is restricted to a volume equal to the previous day's urine output plus measured extrarenal losses (eg, vomitus) plus 500 to 1000 mL/day for insensible loss. Water intake can be further restricted for hyponatremia or increased for hypernatremia. Although weight gain indicates excess fluid, water intake is not decreased if serum Na remains normal; instead, dietary Na is restricted.

Na and K intake is minimized except in patients with prior deficiencies or GI losses. An adequate diet should be provided, including daily protein intake of about 0.8 g/kg. If oral or enteral nutrition is impossible, parenteral nutrition is used; however, in AKI, risks of fluid overload, hyperosmolality, and infection are increased by IV nutrition. Ca salts (carbonate, acetate) or synthetic non–Ca-containing phosphate binders before meals help maintain serum phosphate at < 5 mg/dL (< 1.78 mmol/L). If needed to help maintain serum K at < 6 mmol/L in the absence of dialysis (eg, if other therapies, such as diuretics, fail to lower K), a cation-exchange resin, Na polystyrene sulfonate, is given 15 to 60 g po or rectally 1 to 4 times/day as a suspension in water or in a syrup (eg, 70% sorbitol). An indwelling bladder catheter is rarely needed and should be used only when necessary because of an increased risk of UTI and urosepsis.

In many patients, a brisk and even dramatic diuresis after relief of obstruction is a physiologic response to the expansion of ECF during obstruction and does not compromise volume status. However, polyuria accompanied by the excretion of large amounts of Na, K, Mg, and other solutes may cause hypokalemia, hyponatremia, hypernatremia (if free water is not provided), hypomagnesemia, or marked contraction of ECF volume with peripheral vascular collapse. In this postoliguric phase, close attention to fluid and electrolyte balance is mandatory. Overzealous administration of salt and water after relief of obstruction can prolong diuresis. When postoliguric diuresis occurs, replacement of urine output with 0.45% saline at about 75% of urine output prevents volume depletion and the tendency for excessive free water loss while allowing the body to eliminate excessive volume if this is the cause of the polyuria.

Prevention

AKI can often be prevented by maintaining normal fluid balance, blood volume, and BP in patients with trauma, burns, or severe hemorrhage and in those undergoing major surgery. Infusion of isotonic saline and blood may be helpful. Use of contrast agents should be minimized, particularly in at-risk groups (eg, the elderly and those with preexisting renal insufficiency, volume depletion, diabetes, or heart failure). If contrast agents are necessary, risk can be lowered by minimizing volume of the IV contrast agent, using nonionic and low osmolal or iso-osmolal contrast agents, avoiding NSAIDs, and pretreating with normal saline at 1 mL/kg/h IV for 12 h before the test. Pre- and post-contrast infusion of isotonic $NaHCO_3$ has also been used successfully instead of normal saline. N-acetylcysteine 600 mg po bid the day before and the day of IV contrast administration has been used to prevent contrast nephropathy, but reports of its efficacy are conflicting.

Before cytolytic therapy is initiated in patients with certain neoplastic diseases (eg, lymphoma, leukemia), treatment with rasburicase or allopurinol should be considered along with increasing urine flow by increasing oral or IV fluids to reduce urate crystalluria. Making the urine more alkaline (by giving oral or IV $NaHCO_3$ or acetazolamide) has been recommended by some but is controversial because it may also induce urinary Ca phosphate precipitation and crystalluria, which may worsen AKI.

The renal vasculature is very sensitive to endothelin, a potent vasoconstrictor that reduces renal blood flow and GFR. Endothelin is implicated in progressive renal damage, and endothelin receptor antagonists have successfully slowed or even halted experimental renal disease. Antiendothelin antibodies and endothelin-receptor antagonists are being studied to protect the kidney against ischemic AKI.

Key Points

Causes of AKI can be prerenal (eg, kidney hypoperfusion), renal (eg, direct effects on the kidney), or postrenal (eg, urinary tract obstruction distal to the kidneys).

With AKI, consider ECF volume depletion and nephrotoxins, obtain urinary diagnostic indices and measure bladder residual volume to identify obstruction.

Avoid using IV contrast in imaging studies.

Initiate hemodialysis or hemofiltration as needed for pulmonary edema, hyperkalemia, metabolic acidosis, or uremic symptoms unresponsive to other treatments.

Minimize risk of AKI in patients at risk by maintaining normal fluid balance, avoiding nephrotoxins (including contrast agents) when possible, and taking precautions such as giving fluids or drugs when contrast or cytolytic therapy is necessary.

Equipment: class room, 6-channel ECG machine CARDIOLINE 100 L and Cardioline 200 + II S, ultrasound system Mylab Six CristaLine with 3 detectors.

Lesson time: 2 hours

Plan

I. Organization moments (Greeting, head count, theme announce, aim of lesson, motivating applicants to study the topic).
II. Control of basic knowledges (The task source for self-knowledge skills tests from «KROK2» - additional materials, checking workbooks)

II.1 Requirements for theoretical readiness of applicants to perform practical classes.
Requirements to knowledges:

- Definition of acute kidney injury
- Modern aspects of etiology and pathophysiology of acute kidney injury
- Classification of acute kidney injury
- Clinical manifestation of acute kidney injury
- Laboratory and instrumental investigation of acute kidney injury
- Carry out differential diagnosis of acute kidney injury
- Complications of acute kidney injury
- Treatment, rehabilitation of patients with acute kidney injury
- Prognosis and disability of patients with acute kidney injury

List of didactic units

- To get a detailed anamnesis
- To do physical examination of patient, to diagnose and to estimate changes in condition
- To make a plan of additional investigation and estimate it
- Justify and make a preliminary and clinical diagnoses of acute kidney injury
- Basic principles of treatment acute kidney injury
- Estimation of clinical examination, CBC, blood tests, urinalysis, Nechiporenko`s test, Zimnitsky`s test, kidney ultrasound, CT

II.2 Questions (MSQ, clinical cases) for basic knowledge examination of topic

1. Patient 54 years. Admitted to the Cardiology Department due to suspected myocardial infarction. From history we know that within 3 years of age treated with hemodialysis. Which of the following medications is contraindicated?
A. Enalapril
B. Metaprolol
C. Potassium apartat +
D. Hitroglycerin

E. Candesartan

2. Patient 45 years. Complaints: general weakness, loss of appetite, nausea. In the history - surgical interventions due to calculous cholecystitis, appendectomy. Objective - a state of moderate severity, pale skin, no swelling. BP 150/100 mm Hg, HR 60 bpm. Laboratory tests: a general analysis of urine protein 0.25 g /l, RBC 15-20 in f/v, WBC 3-4 in f/v., gravity 1001; biochemical tests: protein 68 g/l, creatinine 735 mcmol/l, urea 25,5 mmol/l, potassium 6.4, cholesterol 5,1 mmol/l, Hb 72 g/l. Which of the following is a contraindication to treatment by peritoneal dialysis?

A. Creatinine 735 mcmol/l
B. Anemia
C. Hyperpotassiumemia
D. Surgical interventions in anamnesis +
E. Age

3. Patient 28 years. Diabetes mellitus since 7 years old. Complaints about loss of appetite, general weakness, increased blood pressure to 150/110 mmHg. Increases in serum creatinine was revealed 3 years ago. Laboratory tests: a general analysis of urine protein 1.5 g / l, RBC 5-7 in f/v, WBC 15-25 in f/v., gravity 1005; biochemical tests: protein 75 g/l, creatinine 335 mcmol/l, urea 15,5 mmol/l, cholesterol 5,1 mmol/l, glucose 7,5 mmol/l, hemoglobine 92 g/l. What drug is less effective?

A. Enalapril
B. Metaprolol
C. Potassium apartat +
D. Hitroglycerin
E. Candesartan

4. Patient 38 years. Complaints about loss of appetite, general weakness, increased blood pressure to 160/100 mmHg. Increases in serum creatinine was revealed 3 years ago. Laboratory tests: a general analysis of urine protein 1.5 g / l, RBC 5-7 in f/v, WBC 15-25 in f/v., gravity 1005; biochemical tests: protein 75 g/l, creatinine 255 mcmol/l, urea 11,5 mmol/l, cholesterol 5,1 mmol/l, glucose 4,5 mmol/l, hemoglobine 122 g/l. What drug is most effective?

A. Enalapril
B. Metaprolol
C. Potassium apartat
D. Hitroglycerin
E. Candesartan

5. Among the following causes of acute renal failure, the one that would be classified as "postrenal" is:

A . Septicemia
B . Cardiac failure
C. Calculi
D. Rhabdomyolysis +
E. Acute glomerulonephritis

III. Proffesional skills formation (skills of patient`s management, treatment)
Professional algorithms: work with a patient (according to patients-applicants conversation algorithm).

During examination students must use next algorithm:

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Collecting data on patient complains, medical history, life history
5. Interpretation of clinical, laboratory and instrumental studies
6. Explanation for patient of next acting (hospitalization, workup)
7. End of conversation

Physical examination of patient with internal diseases

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Explanation of investigations are needed, taking agreement
5. Telling about possible negative feelings during investigation
6. Preparing to examination (clean warm hands, accurate nails, warm phonendoscope, screen if needed)
7. Examination (demonstration of clinical skills)
8. Interpretation of clinical, laboratory and instrumental studies
9. End of conversation

Telling to patient with internal diseases investigation results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of investigation results
5. Conversation with patient (comparing new and previous examination results, check if explanation is clear)
6. End of conversation

Planning and prognosing treatment results

1. Nice face, smiling
2. Gentle tone of speech
3. Gretting and acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of treatment
5. Conversation with patient (explanation of features taking pills, duration of taking drugs, possible side effects)
6. Check if explanation is clear
7. End of conversation

Telling treatment prognosis

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of expected treatment results
5. Conversation with patient (explanation of importance of life-long treatment, taking medications according to list, check if explanation is
6. clear)
7. End of conversation

Task 1

1. Collecting complains, anamnesis, examination of patients with bronchial asthma
2. Identify clinical and instrumental symptoms
3. Make a syndrome based on symptoms
4. Identify the leading clinical syndrome
5. Assign laboratory and instrumental examination (CBC, urine analysis, blood tests, Nechiporenko test, Zimnitsky`s test, ECG, EchoCG and others)
6. Carry out differential diagnosis with CKD
7. Make a clinical diagnosis
8. Determine a degree of disability

Task 2

Prescribing different variants of treatment according to guidelines

Task 3
Work in Internet, work with thematic literature in department library room.
Applicants must fill patient examination protocol (example is added).

Control materials for final part of the lesson:
1. A 37-year-old patient was brought to resuscitation unit. General condition of the patient is very serious. Sopor. The skin is grey, moist. Turgor is decreased. Pulse is rapid, intense. BP - 160/110 mm Hg, muscle tonus is increased. Hyperreflexia. There is an ammonia odor in the air. What is the presumptive diagnosis?
A Hypoglycemic coma
B Alcoholic coma
C Hyperglycemic coma
D Uraemic coma
E Cerebral coma
2. A 35-year-old patient has been in the intensive care unit for acute renal failure due to crush for 4 days. Objectively: the patient is inadequate. Breathing rate - 32/min. Over the last 3 hours individual moist rales can be auscultated in lungs. ECG shows high T- waves, right ventricular extrasystoles. CVP - 159 mm Hg. In blood: the residual nitrogen - 62 mlmol/l, K^+- 7,1 mlmol/l, Cl^- - 78 millimole/l, Na^+- 120 millimole/l, Ht - 0,32, Hb - 100 g/l, blood creatinine - 0,9 millimole/l. The most appropriate method of treatment would be:
A Hemodialysis
B Plasma sorption
C Hemosorption
D Plasma filtration
E Ultrafiltration
3. A 72 –year-old patient after cholecystectomy was prescribed due to fever gentamicin (80 mg every 8 hours) and cefalotine (2 g every 6 hours). After 10 days was revealed increasing of creatinine level up to 310 mcmol/l. Daily urine output 1200 ml. BP 130/80 mmHg. Urine test – without pathology. US: kidneys size are normal. What is the cause of renal failure?
A Cortical kidney necrosis
B Acute glomerulonephritis
C Nephrotoxic action of gentamicin
D No adequate liquid infusion
E Hepatorenal syndrome
4. Patient after car accident. State severe. BP 80/20 mmHg. During 12 hours urine output 150 ml. What is the cause of renal failure in this case?
A. Degidratation.
B. Urolythiasis.
C. Intoxication.
D. Acute nephritis.
E. Decreasing of BP.
5. Women 55 y.o, due to acute sinusitis gentamicin 80 mg 2 t/daily, i/m, ibuprofen 400 mg / day were prescribed. After 4 days of treatment the patient complains of weakness in the muscles, reducing urine output (200 ml / day), headache, increased blood pressure to 170/100 mmHg. From his youth years- recurrent pyelonephritis. ECG: sinus bradycardia, high sharp T-wave. Your preliminary diagnosis?
A. Chronic pyelonephritis, exacerbation.
B. Chronic renal failure.
C. Complicated hypertensive crisis.
D. Acute renal failure.

E. Acute glomerulonephritis.

6. Patient 20 years old is being treated in the Nephrology Department, complains of anuria over the past 12 hours, back pain, headache, nausea. Acute glomerulonephritis was diagnosed. During urine bladder catheterization was allocated 70 ml brown urine. In blood: creatinine - 276 mcmol/l potassium - 6.5 mmol/l. What complication developed in the patient?
A. Acute renal failure.
B. Acute heart failure.
C. Paralytic urine bladder.
D. Joining of acute pyelonephritis.
E. Joining of urolithiasis.
7. Patient 40 years old, unconscious. According to his wife's words the night before took 300 ml of alcohol unspecified origin. In the blood: Hb - 100 g/ , ESR - 32 mm/h, creatinine - 468 mcmol/l, potassium - 6.9 mmol/l. Uremic coma was diagnosed. What should you do?
A. Artificial ventilation of lungs..
B. Forced diuresis..
C. Assign cardiac glycosides.
D. Hemodialysis.
E. Assign sodium nitroprusside..
8. A 23-year-old patient after intake of brake fluid has developed anuria that has been lasting for 5 days already. Creatinine level increased up to 0,769 mmol/l. What treatment tactics should be chosen in the given case?
A. Hemodialysis

B. Detoxification therapy
C. Antidotal therapy
D. Diuretics
E. Plasmapheresis
9. Patient 20 years old, is being treated in the Nephrology department, complains of anuria, back pain, headache, nausea. Felt ill 2 days ago. Illness began with pain in the lower back, fever, headache, reduced amount of urine, the appearance of red urine. Two weeks ago, suffered scarlet fever. At the time of inspection BP 170/120 mmHg, HR 90 bpm. In the blood: Hb - 102 g/ l, ESR - 30 mm/h. What is the most probable cause of anuria in this case?
A. Renal amyloidosis.
B. Acute glomerulonephritis.
C. Acute pyelonephritis.
D. Urolithiasis.
E. Interstitial nephritis.
10. Patient 20 years old is being treated in the Nephrology Department, complains of anuria over the past 12 hours, back pain, headache, nausea. Acute glomerulonephritis was diagnosed. During urine bladder catheterization was allocated 70 ml brown urine. In blood: creatinine - 276 mcmol/l potassium - 6.5 mmol/l. What complication developed in the patient?
A. Paralytic urine bladder.
B. Acute heart failure.
C. Acute renal failure.
D. Joining of acute pyelonephritis.
E. Joining of urolithiasis.

Standard answers: 1-D, 2-A, 3-C, 4-D, 4-E, 5-D, 6-A, 7-D, 8-A, 9-B, 10-C.

B. Clinical case with answers
1. Patient 27 years, has called a brigade ambulance due to a sharp deterioration. Worried about a severe headache, dizziness, nausea, vomiting, noted a sharp decrease the number of allocated urine - less than 200 ml per day, the urine saturated red color. Last night urine does not come off.

Two days ago the morning drew attention to the swelling of subcutaneous fat tissue under the eyes, noted the decrease in amount of urine, change its color. Anamnesis - two weeks ago, recovered from lacunary angina. Treated by himself - took acetylsalicylic acid.
On examination: skin pale, edema under the eyes. Pulse the same on both hands, rhythmic, intense, HR 102 in 1 min, BP 160/110 mmHg. In the lungs vesicular breathing. Stabbing on lumbar region - pain on both sides. There is a little pasty feet.
1. Primary clinical diagnosis.
2. Plan of investigation.
3. Treatment.
Answering standards
1. Acute glomerulonephritis with arterial hypertension. Acute renal failure.
2. CBC, urine, Nechiporenko, Zimnitskiy tests. Blood: non-specific inflammation, ASLO, CRP, the definition of acid-base balance, total protein and protein fractions, lipid profile, coagulation blood electrolytes, urea, creatinine. GFR. Immunological tests: Immune changes, elevated levels of circulating immune complexes. ECG. Ultrasound of the kidneys.
3. Hemodialyse.
2. Patient A., aged 36, delivered to the therapeutic department for urgent indications on the second day of illness with a diagnosis of bilateral outhospital pneumonia. The illness began badly, with chills, fever up to 39.00 C, pain in the right lumbar region, through the night joined a cough, initially dry, then moist with purulent sputum, dyspnea at rest, severe weakness, nausea, vomiting, dizziness, stupor consciousness, the last day the patient has provided no more than 300 ml urine.
On admission: the patient is inhibited, hardly comes into contact. Skin and visible mucous pale, bloated face. Pulse 108 beats per minute, regular, satisfactory properties. BP 90/70 mmHg. Cardiac dullness in the normal range. Heart sounds are muffled, rhythmic. Delay of the right half of the chest during the act of breathing, dulness of percussion sounds and weakening vesicular breathing in the lower parts of lungs more pronounced on the right, right - below the angle of scapula breath does not listen. RR-32 in a minute. The abdomen was soft and painless. Stabbing on lumbar region – no pain.
Chest X-ray revealed bilateral lower lobe pneumonia, right-sided pleurisy. CBC: Hb-109 g / l, E .- 3.8×10^{12}/l.L. - 12.0×10^{9} / l, e - 1%, ban - 12%, s - 70%, lymph - 15%, m - 2%, ESR - 24 mm / hour. Creatinine blood-0.346 mmol / l.
1. Primary clinical diagnosis.
2. Plan of additional investigation
3. Treatment.
Answering standards
1. Outhospital lower lobe pneumonia, severe course. Right-sided pleurisy. Infectious-toxic shock. Acute renal failure, moderate, oligoanuric stage.
2. Nechiporenko, Zimnitskiy tests, the definition of bacteriuria, acid-base balance, control of daily diuresis, total protein and protein fractions, lipidogramme, coagulation, renal ultrasound, consulting ophthalmologist, ECG. GFR.Sputum and hemoculture of blood.
3. Intensive care unit, diet poor protein, correction of acid-base balance, electrolyte disorders, detoxication and antiinflammatory therapy, antibiotics, mucolytics, correction of low cardiac output, dopamine, hemodialysis.

IV. Making conclusions, telling final marks, tasks for the next lesson

Literature list

1. 1. Harrison's Manual in Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 1245 p.
2. Harrison's Principles of Internal Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 3528 p.
3. BMJ Best Practice. Acute kidney injury. - BMJ publishing group LTD, 2019. – 53 p.

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European male of 48 years old.

Complaints: nausea, vomiting, weakness, fatigue, anuria within 12 hours, puffy face.

Medical history: According to the patient, the condition worsened about 1 week ago, when, after a cold he started to feel chills. After several hours patient starts to feel fatigue. On next day he mentioned that he had a headache and pain in right lumbar area, his urine started to be cloudy, but he didn`t called a doctor. At the present time patient went to the clinic in connection with the persisting complaints described above. Hospitalization is strongly recommended.

Life history: Patient doesn't have any another pathology.

Allergic history is not burdened.

Hereditary history: mother suffers from chronic cystitis.

Epidemiological anamnesis: Hepatitis, tuberculosis, malaria, helminthiasis, candidiasis, blood transfusion for the last 3 months, the passage of the segments of the worms denies. He has not been abroad for the last 12 months.

Bad habits: denies

Objective status: General condition of moderate severity. Normosthenic constitution, satisfactory nutrition. Height 168 cm Weight - 80 kg.

The skin and visible mucous membranes are clean, pale pink.

The thyroid gland and peripheral lymph nodes are not enlarged.

Breathing over the lungs is vesicular, no wheezing. Percussion - clear pulmonary sound. Breath rate = 21/ min.

BP –110/70 mm Hg symmetrical on both hands. Heart rhythm is regular, heart rate – 1 3beats. in 1 min. Heart sounds are clear.

Tongue moist, coated with white bloom. The abdomen is soft and painless on palpation. The liver and spleen are not palpable.

The symptom of tapping over the projection of the kidneys is positive on boh side. Edema on legs and face

Diagnosis: Acute pyelonephritis. Acute kidney injury. Anuria.

Examination plan:

1. Cell blood count,
2. blood biochemistry: creatinine, urea
3. coagulation test,
4. liver function tests,
5. lipid profile
6. Potassium, sodium
7. Blood gases
8. urinalysis, Nechiporenko`s test;
9. Kidney ultrasound
10. ECG

Treatment plan:

1. Bed rest, nephrologic diet with a reduction of protein and salt, control of diuresis
2. Ceftriaxone 1,0 g intravenous, in morning and in the evening
3. Levofloxacine 500 mg intravenous, in morning
4. Omeprazole 20 mg 2 times a day, orally, before breakfast and before lunch
5. Caps. «Diurol» orally, in morning and in the evening, after meal
6. Paracetamol 1000 mg intravenous 1 time per day
7. NaCL 0.9% 200-400 ml intravenous
8. Furosemide 40-100 mg intravenous
9. In case of treatment failed - dialysis

Practical lesson № 20
Topic 12: Chronic obstructive pulmonary disease

Object: To teach applicants to master the method of examination of patients with respiratory diseases with the selection of the main pulmonological syndromes. To study probable etiological factors, pathogenesis of chronic obstructive pulmonary diseases, their main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis and efficiency of patients.

Basic concepts:

№	Term	Definition
1	Emphysema	destruction of the gas-exchanging surfaces of the lung (alveoli).
2	Chronic bronchitis	the presence of cough and sputum production for at least 3 months in each of two consecutive years.
3	Spirometry	is the most common of the pulmonary function tests (PFTs). Measure the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC) and the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second, FEV1), and the ratio of these two measurements (FEV1/FVC) should be calculated.
4	Tiffeneau-Pinelli index	The FEV1/FVC ratio, used in the diagnosis of obstructive and restrictive lung disease. The diagnosis of airway obstruction is made when the FEV1/FVC ratio is less than 0.7
5	Broncho-obstructive syndrome	is a pathological condition with airflow limitation during breathing. Airway obstruction consists of reversible and irreversible components.
6	SABA	Short-acting B2-agonists - medications that relax airway smooth muscle by stimulating beta2- adrenergic receptors, works for 4-6 hours
7	LABA	Long-acting B2-agonists - medications that relax airway smooth muscle by stimulating beta2- adrenergic receptors, works for 12 or more hours
8	SAMA	Short-acting muscarinic antagonists - medications block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle
9	LAMA	Long-acting muscarinic antagonists - medications block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle, with prolonged duration of bronchodilator effect

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.

Chronic Obstructive Pulmonary Disease (COPD) is an increasingly recognized cause of morbidity and mortality. Over the next 10 years, deaths due to COPD are expected to increase by 30% and, by 2030, COPD is estimated to be the third leading cause of death worldwide.

Etiology

There are several causes of COPD:

- Smoking (and less often other inhalational exposures)
- Genetic factors

Inhalational exposure:

Of all inhalational exposures, cigarette smoking is the primary risk factor in most countries, although only about 15% of smokers develop clinically apparent COPD; an exposure history of 40 or more pack-years is especially predictive.

Low body weight, childhood respiratory disorders, and exposure to passive cigarette smoke, air pollution, and occupational dust (eg, mineral dust, cotton dust) or inhaled chemicals (eg, cadmium) contribute to the risk of COPD but are of minor importance compared with cigarette smoking.

Genetic factors:

The best-defined causative genetic disorder is α_1-antitrypsin deficiency, which is an important cause of emphysema in nonsmokers and influences susceptibility to disease in smokers.

Pathophysiology

Various factors cause the airflow limitation and other complications of COPD.

Inflammation:

Inhalational exposures can trigger an inflammatory response in airways and alveoli that leads to disease in genetically susceptible people. The inflammation in COPD increases as disease severity increases, and, in severe (advanced) disease, inflammation does not resolve completely despite smoking cessation. This chronic inflammation does not seem to respond to corticosteroids.

Infection:

Respiratory infection (which COPD patients are prone to) may amplify progression of lung destruction.

Airflow limitation:

The cardinal pathophysiologic feature of COPD is airflow limitation caused by airway obstruction, loss of elastic recoil, or both.

Airway obstruction is caused by inflammation-mediated mucus hypersecretion, mucus plugging, mucosal edema, bronchospasm, peribronchial fibrosis, or a combination of these mechanisms.

Complications:

In addition to airflow limitation and sometimes respiratory insufficiency, complications include

- Pulmonary hypertension
- Respiratory infection
- Weight loss and other comorbidities

Chronic hypoxemia increases pulmonary vascular tone, which, if diffuse, causes pulmonary hypertension and cor pulmonale.

Viral or bacterial respiratory infections are common among patients with COPD and cause a large percentage of acute exacerbations.

Weight loss may occur, perhaps in response to decreased caloric intake and increased levels of circulating tumor necrosis factor (TNF)-α.

Other coexisting or complicating disorders that adversely affect quality of life and survival include osteoporosis, depression, coronary artery disease, lung cancer, muscle atrophy, and gastroesophageal reflux.

Symptoms and Signs

COPD takes years to develop and progress. Most patients have smoked ≥ 20 cigarettes/day for > 20 yr. Productive cough usually is the initial symptom, developing among smokers in their 40s and 50s. Dyspnea that is progressive, persistent, exertional, or worse during respiratory infection appears when patients are in their late 50s or 60s. Symptoms usually progress quickly in patients who continue to smoke and in those who have a higher lifetime tobacco exposure. Morning headache develops in more advanced disease and signals nocturnal hypercapnia or hypoxemia.

Acute exacerbations occur sporadically during the course of COPD and are heralded by increased symptom severity. The specific cause of any exacerbation is almost always impossible to determine, but exacerbations are often attributed to viral URIs, acute bacterial bronchitis, or exposure to respiratory irritants. As COPD progresses, acute exacerbations tend to become more frequent, averaging about 1 to 3 episodes/yr.

Signs of COPD include wheezing, increased expiratory phase of breathing, lung hyperinflation manifested as decreased heart and lung sounds, and increased anteroposterior diameter of the thorax (barrel chest). Patients with advanced emphysema lose weight and experience muscle wasting that has been attributed to immobility, hypoxia, or release of systemic inflammatory mediators, such as TNF-α. Signs of advanced disease include pursed-lip breathing, accessory muscle use, paradoxical inward movement of the lower intercostal interspaces during inspiration (Hoover sign), and cyanosis. Signs of cor pulmonale include neck vein distention, splitting of the 2nd heart sound with an accentuated pulmonic component, tricuspid insufficiency murmur, and peripheral edema. Right ventricular heaves are uncommon in COPD because the lungs are hyperinflated.

Spontaneous pneumothorax may occur (possibly related to rupture of bullae) and should be suspected in any patient with COPD whose pulmonary status abruptly worsens.

Diagnosis

- Chest x-ray
- Pulmonary function testing

Diagnosis is suggested by history, physical examination, and chest imaging and is confirmed by pulmonary function tests. Similar symptoms can be caused by asthma, heart failure, and bronchiectasis. COPD and asthma are sometimes easily confused.

Differential Diagnosis of COPD

Systemic disorders that may have a component of airflow limitation may suggest COPD; they include HIV infection, abuse of IV drugs (particularly cocaine and amphetamines), sarcoidosis, Sjögren syndrome, bronchiolitis obliterans, lymphangioleiomyomatosis, and eosinophilic granuloma. COPD can be differentiated from interstitial lung diseases (ILD) by chest imaging, which shows increased interstitial markings in ILD, and pulmonary function testing, which shows a restrictive ventilatory defect rather than an obstructive ventilatory defect. In some patients, COPD and ILD coexist (combined pulmonary fibrosis and emphysema [CPFE]) in which lung volumes are relatively preserved, but gas exchange is severely impaired.

Pulmonary function tests:

Patients suspected of having COPD should undergo complete pulmonary function testing to confirm airflow limitation, to quantify its severity and reversibility, and to distinguish COPD from other disorders. Pulmonary function testing is also useful for following disease progression and monitoring response to treatment. The primary diagnostic tests are

- FEV_1, which is the volume of air forcefully expired during the first second after taking a full breath
- Forced vital capacity (FVC), which is the total volume of air expired with maximal force
- Flow-volume loops, which are simultaneous spirometric recordings of airflow and volume during forced maximal expiration and inspiration

Reductions of FEV_1, FVC, and the ratio of FEV_1/FVC are the hallmark of airflow limitation.

Additional pulmonary function testing is necessary only in specific circumstances, such as before lung volume reduction surgery. Other test abnormalities may include increased total lung capacity, functional residual capacity, and residual volume, which can help distinguish COPD from

restrictive pulmonary disease, in which these measures are diminished; decreased vital capacity; and decreased single-breath diffusing capacity for carbon monoxide (DL_{CO}). Decreased DL_{CO} is nonspecific and is reduced in other disorders that affect the pulmonary vascular bed, such as interstitial lung disease, but can help distinguish emphysema from asthma, in which DL_{CO} is normal or elevated.

Classification and Treatment of COPD

Patient Group	Findings	Treatment	Alternative Treatments
All patients	—	Avoidance of risk factors (eg, smoking) Influenza vaccine annually Pneumococcal polysaccharide vaccine Treatment of complications	—
A (low risk, few symptoms)	FEV_1 > 50% predicted 0–1 exacerbation/yr MRCDS*: 0–1	SABA or SAC, as needed	LAC or LABA or SABA plus SAC
B (low risk, more symptoms)	FEV_1 > 50% predicted 0–1 exacerbation/yr MRCDS ≥ 2	LAC or LABA	LABA plus LAC or SABA plus SAC
C (high risk, few symptoms)	FEV_1 < 50% predicted ≥ 2 exacerbations/yr MRCDS: 0–1	ICS plus LABA or LAC	LABA plus LAC
D (high risk, more symptoms)	FEV_1 < 50% predicted ≥ 2 exacerbations/yr MRCDS: ≥ 2	ICS plus LABA or LAC	ICS plus LAC or ICS plus LABA plus LAC or ICS plus LABA plus PDE4I or LABA plus LAC or LAC plus PDE4I
*The COPD Assessment Test (CAT) may be used instead of the MRCDS to evaluate symptoms. For MRC definitions, see see Modified Medical Research Council Dyspnea Scale.			
FEV_1 = forced expiratory volume in 1 sec; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LAC = long-acting anticholinergic; MRCDS = Medical Research Council dyspnea scale; PDE4I = phosphodiesterase-4 inhibitor; SABA = short-acting β-agonist; SAC = short-acting anticholinergic.			

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.

Imaging tests:

Chest x-ray may have characteristic findings. In patients with emphysema, changes can include lung hyperinflation manifested as a flat diaphragm, rapid tapering of hilar vessels, and bullae. Other typical findings include widening of the retrosternal airspace and a narrow cardiac shadow. Emphysematous changes occurring predominantly in the lung bases suggest α_1-antitrypsin deficiency. The lungs may look normal or have increased lucency secondary to loss of parenchyma. Among patients with chronic obstructive bronchitis, chest x-rays may be normal or may show a bibasilar increase in bronchovascular markings as a result of bronchial wall thickening. Prominent hila suggest large central pulmonary arteries that may signify pulmonary hypertension. Right ventricular enlargement that occurs in cor pulmonale may be masked by lung hyperinflation or may manifest as encroachment of the heart shadow on the retrosternal space or by widening of the transverse cardiac shadow in comparison with previous chest x-rays.

Chest CT may reveal abnormalities that are not apparent on the chest x-ray and may also suggest coexisting or complicating disorders, such as pneumonia, pneumoconiosis, or lung cancer. CT helps assess the extent and distribution of emphysema, estimated either by visual scoring or with analysis of the distribution of lung density. Indications for obtaining CT in patients with COPD include evaluation for lung volume reduction surgery, suspicion of coexisting or complicating disorders that are not clearly evident or excluded by chest x-ray, and suspicion of cancer.

Adjunctive tests:

α_1-Antitrypsin levels should be measured in patients < 50 yr with symptomatic COPD and in nonsmokers of any age with COPD to detect α_1-antitrypsin deficiency. Other indications of α_1-antitrypsin deficiency include a family history of premature COPD or unexplained liver disease, lower-lobe distribution of emphysema, and COPD associated with antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis. If levels of α_1-antitrypsin are low, the diagnosis should be confirmed by genetic testing to establish the α_1-antitrypsin phenotype.

ECG, often done to exclude cardiac causes of dyspnea, typically shows diffusely low QRS voltage with a vertical heart axis caused by lung hyperinflation and increased P-wave voltage or rightward shifts of the P-wave vector caused by right atrial enlargement in patients with advanced emphysema. Findings of right ventricular hypertrophy include an R or R′ wave as tall as or taller than the S wave in lead V_1; an R wave smaller than the S wave in lead V_6; right-axis deviation > 110° without right bundle branch block; or some combination of these. Multifocal atrial tachycardia, an arrhythmia that can accompany COPD, manifests as a tachyarrhythmia with polymorphic P waves and variable PR intervals.

Echocardiography is occasionally useful for assessing right ventricular function and pulmonary hypertension, although air trapping makes it technically difficult in patients with COPD. Echocardiography is most often indicated when coexistent left ventricular or valvular heart disease is suspected.

CBC is of little diagnostic value in the evaluation of COPD but may show erythrocythemia (Hct > 48%) if the patient has chronic hypoxemia. Patients with anemia (for reasons other than COPD) have disproportionately severe dyspnea. Serum electrolytes are of little value but may show an elevated HCO_3 level if patients have chronic hypercapnia.

Evaluation of exacerbations:

Patients with acute exacerbations usually have combinations of increased cough, sputum, dyspnea, and work of breathing, as well as low O_2 saturation on pulse oximetry, diaphoresis, tachycardia,

anxiety, and cyanosis. However, patients with exacerbations accompanied by retention of CO_2 may be lethargic or somnolent, a very different appearance. All patients requiring hospitalization for an acute exacerbation should undergo testing (eg, ABG sampling) to quantify hypoxemia and hypercapnia. Hypercapnia may exist without hypoxemia.

Findings of $PaO_2 < 50$ mm Hg or $PaCO_2 > 50$ mm Hg in the setting of respiratory acidemia define acute respiratory failure. However, some patients chronically manifest such levels of PaO_2 and $PaCO_2$ in the absence of acute respiratory failure.

A chest x-ray is often done to check for pneumonia or pneumothorax. Very rarely, among patients receiving chronic systemic corticosteroids, infiltrates may represent Aspergillus pneumonia.

Yellow or green sputum is a reliable indicator of neutrophils in the sputum and suggests bacterial colonization or infection. Culture is usually done in hospitalized patients but is not usually necessary in outpatients. In samples from outpatients, Gram stain usually shows neutrophils with a mixture of organisms, often gram-positive diplococci (Streptococcus pneumoniae), gram-negative bacilli (H. influenzae), or both. Other oropharyngeal commensal organisms, such as Moraxella (Branhamella)catarrhalis, occasionally cause exacerbations. In hospitalized patients, cultures may show resistant gram-negative organisms (eg, Pseudomonas) or, rarely, Staphylococcus.

Prognosis

Severity of airway obstruction predicts survival in patients with COPD. The mortality rate in patients with an $FEV_1 \geq 50\%$ of predicted is slightly greater than that of the general population. If the FEV_1 is 0.75 to 1.25 L, 5-yr survival is about 40 to 60%; if < 0.75 L, about 30 to 40%.

More accurate prediction of death risk is possible by simultaneously measuring body mass index (B), the degree of airflow obstruction (O, which is the FEV_1), dyspnea (D, which is measured with a Modified Medical Research Council [MMRC] dyspnea scale, and exercise capacity (E, which is measured with a 6-min walking test); this is the BODE index. Also, older age, heart disease, anemia, resting tachycardia, hypercapnia, and hypoxemia decrease survival, whereas a significant response to bronchodilators predicts improved survival. Risk factors for death in patients with acute exacerbation requiring hospitalization include older age, higher $PaCO_2$, and use of maintenance oral corticosteroids.

Patients at high risk of imminent death are those with progressive unexplained weight loss or severe functional decline (eg, those who experience dyspnea with self-care, such as dressing, bathing, or eating). Mortality in COPD may result from intercurrent illnesses rather than from progression of the underlying disorder in patients who have stopped smoking. Death is generally caused by acute respiratory failure, pneumonia, lung cancer, heart disease, or pulmonary embolism.

Treatment of Stable COPD

- Inhaled bronchodilators, corticosteroids, or both
- Supportive care (eg, smoking cessation, O_2 therapy, pulmonary rehabilitation)

COPD management involves treatment of chronic stable disease and of exacerbations. Treatment of cor pulmonale, a common complication of long-standing, severe COPD, is discussed elsewhere.

Treatment of chronic stable COPD aims to prevent exacerbations and improve lung and physical function through drug and O_2 therapy, smoking cessation, exercise, enhancement of nutrition, and pulmonary rehabilitation. Surgical treatment of COPD is indicated for selected patients.

Drug therapy.

Inhaled bronchodilators are the mainstay of COPD management; drugs include

- β-agonists
- Anticholinergics (antimuscarinics)

These two classes are equally effective. Patients with mild (group A) disease are treated only when symptomatic. Those in groups B, C, or D COPD should be taking drugs from one or both of these classes regularly to improve pulmonary function and increase exercise capacity. The frequency of exacerbations can be reduced with the use of anticholinergics, inhaled corticosteroids, or long-actingβ-agonists. However, there is no evidence that regular bronchodilator use slows deterioration

of lung function. The initial choice among short-acting β-agonists, long-acting β-agonists, anticholinergics (which have a greater bronchodilating effect), and combination β-agonist and anticholinergic therapy is often a matter of tailoring cost and convenience to the patient's preferences and symptoms.

For home treatment of chronic stable disease, drug administration by metered-dose inhaler or dry-powder inhaler is preferred over administration by nebulizer; home nebulizers are prone to contamination due to incomplete cleaning and drying. Therefore, nebulizers should be reserved for people who cannot coordinate activation of the metered-dose inhaler with inhalation or cannot develop enough inspiratory flow for dry powder inhalers. For metered-dose inhalers, patients should be taught to exhale to functional residual capacity, inhale the aerosol slowly to total lung capacity, and hold the inhalation for 3 to 4 sec before exhaling. Spacers help ensure optimal delivery of drug to the distal airways and reduce the importance of coordinating activation of the inhaler with inhalation. Some spacers alert patients if they are inhaling too rapidly. Newer metered-dose inhalers that use hydrofluoroalkane (HFA) propellants require slightly different techniques than inhalers containing older environmentally damaging chlorinated fluorocarbon propellants; inhalers containing HFA require 2 to 3 priming doses if they are new or not recently used.

β-Agonists relax bronchial smooth muscle and increase mucociliary clearance. Albuterol aerosol, 2 puffs (90 to 100 mcg/puff) inhaled from a metered-dose inhaler 4 to 6 times/day prn, is usually the drug of choice because of low cost. Long-acting β-agonists are preferable for patients with nocturnal symptoms or for those who find frequent dosing inconvenient. Options include salmeterol powder, 1 puff (50 mcg) inhaled bid, indacaterol 1 puff (75 mcg) inhaled once/day (150 mcg once/day in Europe), and formoterol powder, 1 puff (12 mcg) inhaled bid. The dry-powder formulations may be more effective for patients who have trouble coordinating use of a metered-dose inhaler. Patients should be taught the difference between short-acting and long-acting drugs, because long-acting drugs that are used as needed or more than twice/day increase the risk of cardiac arrhythmias. Adverse effects commonly result from use of any β-agonist and include tremor, anxiety, tachycardia, and mild, temporary hypokalemia.

Anticholinergics (antimuscarinics) relax bronchial smooth muscle through competitive inhibition of muscarinic receptors (M_1, M_2, and M_3). Ipratropium is a short-acting anticholinergic; dose is 2 to 4 puffs (18 mcg/puff) from a metered-dose inhaler q 4 to 6 h. Ipratropium has a slower onset of action (within 30 min; peak effect in 1 to 2 h), so a β_2-agonist is often prescribed with it in a single combination inhaler or as a separate as-needed rescue drug. Tiotropium is a long-acting quaternary anticholinergic inhaled as a powder formulation. Dose is 1 puff (18 mcg) once/day. Aclidinium bromide is available as a multidose dry-powder inhaler. Dose is 1 puff (400 mcg/puff) bid. Adverse effects of all anticholinergics are pupillary dilation (and risk of triggering or worsening acute angle closure glaucoma), urinary retention, and dry mouth.

Corticosteroids are often part of treatment. Inhaled corticosteroids seem to reduce airway inflammation, reverse β-receptor down-regulation, and inhibit leukotriene and cytokine production. They do not alter the course of pulmonary function decline in patients with COPD who continue to smoke, but they do relieve symptoms and improve short-term pulmonary function in some patients, are additive to the effect of bronchodilators, and may diminish the frequency of COPD exacerbations. They are indicated for patients who have repeated exacerbations or symptoms despite optimal bronchodilator therapy. Dose depends on the drug; examples include fluticasone 500 to 1000 mcg/day andbeclomethasone 400 to 2000 mcg/day. The long-term risks of inhaled corticosteroids in elderly people are not proved but probably include osteoporosis, cataract formation, and an increased risk of nonfatal pneumonia. Long-term users therefore should undergo periodic ophthalmologic and bone densitometry screening and should possibly receive supplemental calcium, vitamin D, and a bisphosphonate as indicated. Corticosteroid therapy should be stopped if no subjective or objective improvement results (eg, after a few months).

Combinations of a long-acting β-agonist (eg, salmeterol) and an inhaled corticosteroid (eg,fluticasone) are more effective than either drug alone in the treatment of chronic stable disease.

Oral or systemic corticosteroids should usually not be used to treat chronic stable COPD.

Theophylline plays only a small role in the treatment of chronic stable COPD now that safer, more effective drugs are available. Theophylline decreases smooth muscle spasm, enhances mucociliary clearance, improves right ventricular function, and decreases pulmonary vascular resistance and arterial pressure. Its mode of action is poorly understood but appears to differ from that of β_2-agonists and anticholinergics. Its role in improving diaphragmatic function and dyspnea during exercise is controversial. Low-dose oral theophylline (300 to 400 mg/day) has anti-inflammatory properties and may enhance the effects of inhaled corticosteroids.

Theophylline can be used for patients who have not adequately responded to inhaled drugs and who have shown symptomatic benefit from a trial of the drug. Serum levels need not be monitored unless the patient does not respond to the drug, develops symptoms of toxicity, or is questionably adherent; slowly absorbed oral theophylline preparations, which require less frequent dosing, enhance adherence. Toxicity is common and includes sleeplessness and GI upset, even at low blood levels. More serious adverse effects, such as supraventricular and ventricular arrhythmias and seizures, tend to occur at blood levels > 20 mg/L. Hepatic metabolism of theophylline varies greatly and is influenced by genetic factors, age, cigarette smoking, hepatic dysfunction, and some drugs, such as macrolide and fluoroquinolone antibiotics and nonsedating histamine$_2$ blockers.

Phosphodiesterase-4 inhibitors are more specific than theophylline for pulmonary phosphodiesterase and have fewer adverse effects. They have anti-inflammatory properties and are mild bronchodilators. Phosphodiesterase-4 inhibitors include roflumilast and cilomilast, but roflumilast is the only one in routine clinical use. It can be used in addition to other bronchodilators for reduction of exacerbations in patients with COPD. The dose is 500 mcg po once/day. Common adverse effects include nausea, headache, and weight loss, but these effects may subside with continued use.

O_2 therapy:

Long-term O_2 therapy prolongs life in patients with COPD whose Pa_{O_2} is chronically < 55 mm Hg. Continual 24-h use is more effective than a 12-h nocturnal regimen. O_2 therapy brings Hct toward normal levels; improves neuropsychologic factors, possibly by facilitating sleep; and ameliorates pulmonary hemodynamic abnormalities. O_2 therapy also increases exercise tolerance in many patients.

O_2 saturation should be measured during exercise and while at rest. Similarly, a sleep study should be considered for patients with advanced COPD who do not meet the criteria for long-term O_2 therapy while they are awake but whose clinical assessment suggests pulmonary hypertension in the absence of daytime hypoxemia. Nocturnal O_2may be prescribed if a sleep study shows episodic desaturation to $\leq$ 88%. Such treatment prevents progression of pulmonary hypertension, but its effects on survival are unknown.

O_2 is administered by nasal cannula at a flow rate sufficient to achieve a Pa_{O_2} > 60 mm Hg (Sa_{O_2}>90%), usually $\leq$ 3 L/min at rest. O_2 is supplied by electrically driven O_2 concentrators, liquid O_2systems, or cylinders of compressed gas. Concentrators, which limit mobility but are the least expensive, are preferable for patients who spend most of their time at home. Such patients require small O_2 tanks for backup in case of an electrical failure and for portable use.

A liquid system is preferable for patients who spend much time out of their home. Portable canisters of liquid O_2 are easier to carry and have more capacity than portable cylinders of compressed gas. Large compressed-air cylinders are the most expensive way of providing O_2 and should be used only if no other source is available. All patients must be taught the dangers of smoking during O_2 use.

Various O_2-conserving devices can reduce the amount of O_2 used by the patient, either by using a reservoir system or by permitting O_2 flow only during inspiration. Systems with these devices correct hypoxemia as effectively as do continuous flow systems.

Some patients need supplemental O_2 during air travel, because flight cabin pressure in commercial airliners is below sea level air pressure (often equivalent to 1830 to 2400 m [6000 to 8000 ft]). Eucapnic COPD patients who have a Pa_{O_2} > 68 mm Hg at sea level generally have an in-flight Pa_{O_2} > 50 mm Hg and do not require supplemental O_2. All patients with COPD with a $Pa_{O_2} \leq$ 68

mm Hg at sea level, hypercapnia, significant anemia (Hct < 30), or a coexisting heart or cerebrovascular disorder should use supplemental O_2 during long flights and should notify the airline when making their reservation. Airlines can provide supplemental O_2, and most require a minimum notice of 24 h, a physician's statement of necessity, and an O_2 prescription before the flight. Patients should bring their own nasal cannulas, because some airlines provide only face masks. Patients are not permitted to transport or use their own liquid O_2, but many airlines now permit use of portable battery-operated O_2concentrators, which also provide a suitable O_2 source on arrival.

Indications for Long-Term O 2 Therapy in COPD
Pa o $_2 \leq$ 55 mm Hg or Sa o $_2 \leq$ 88%* in patients receiving optimal medical regimen for at least 30 days †
Pa o $_2$ = 55 to 59 mm Hg or Sa o $_2 \leq$ 89%* for patients with cor pulmonale or erythrocytosis (Hct > 55%)
Can be considered for Pa o $_2 \geq$ 60 mm Hg or Sa o $_2 \geq$ 90%* for patients whose room-air Pa o $_2$ is $\leq$ 55 mm Hg or Sa o $_2 \leq$ 88% during exercise or sleep

Smoking cessation:

Smoking cessation is both extremely difficult and extremely important; it slows but does not halt the rate of FEV_1 decline. Simultaneous use of multiple strategies is most effective: establishment of a quit date, behavior modification techniques, group sessions, nicotine replacement therapy (by gum, transdermal patch, inhaler, lozenge, or nasal spray), varenicline or bupropion (wellbutrin, zyban), and physician encouragement. Quit rates > 50% at 1 yr have not been demonstrated even with the most effective interventions, such as use of bupropion combined with nicotine replacement or use of varenicline alone.

Vaccinations:

All patients with COPD should be given annual influenza vaccinations. If a patient is unable to receive a vaccination or if the prevailing influenza strain is not included in the annual vaccine formulation, prophylactic treatment with a neuraminidase inhibitor (oseltamivir or zanamivir) is sometimes used if there is close exposure to influenza-infected people. Treatment with a neuraminidase inhibitor should be started at the first sign of an influenza-like illness. Pneumococcal polysaccharide vaccine, although of unproven efficacy in COPD, has minimal adverse effects and should probably also be given.

Nutrition:

COPD patients are at risk of weight loss and nutritional deficiencies because of a higher energy cost of daily activities; reduced caloric intake relative to need because of dyspnea; and the catabolic effect of inflammatory cytokines such as TNF-α. Generalized muscle strength and efficiency of O_2 use are impaired. Patients with poorer nutritional status have a worse prognosis, so it is prudent to recommend a balanced diet with adequate caloric intake in conjunction with exercise to prevent or reverse undernutrition and muscle atrophy. However, excessive weight gain should be avoided, and obese patients should strive to gradually reduce body fat. Studies of nutritional supplementation alone have not shown improvement in pulmonary function or exercise capacity. Trials of appetite stimulants, anabolic steroids, growth hormone supplementation, and TNF antagonists in reversing undernutrition and improving functional status and prognosis in COPD have been disappointing.

Pulmonary rehabilitation:

Pulmonary rehabilitation programs serve as adjuncts to drug treatment to improve physical function; many hospitals and health care organizations offer formal multidisciplinary rehabilitation programs. Pulmonary rehabilitation includes exercise, education, and behavioral interventions. Treatment should be individualized; patients and family members are taught about COPD and medical treatments, and patients are encouraged to take as much responsibility for personal care as

possible. The benefits of rehabilitation are greater independence and improved quality of life and exercise capacity. Pulmonary rehabilitation typically does not improve pulmonary function. A carefully integrated rehabilitation program helps patients with severe COPD accommodate to physiologic limitations while providing realistic expectations for improvement. Patients with severe disease require a minimum of 3 mo of rehabilitation to benefit and should continue with maintenance programs.

An exercise program can be helpful in the home, in the hospital, or in institutional settings. Graded exercise can ameliorate skeletal muscle deconditioning resulting from inactivity or prolonged hospitalization for respiratory failure. Specific training of respiratory muscles is less helpful than general aerobic conditioning.

A typical training program begins with slow walking on a treadmill or unloaded cycling on an ergometer for a few minutes. Duration and exercise load are progressively increased over 4 to 6 wk until the patient can exercise for 20 to 30 min nonstop with manageable dyspnea. Patients with very severe COPD can usually achieve an exercise regimen of walking for 30 min at 1 to 2 mph. Maintenance exercise should be done 3 to 4 times/wk to maintain fitness levels. O_2 saturation is monitored, and supplemental O_2 is provided as needed.

Upper extremity resistance training helps the patient in doing daily tasks (eg, bathing, dressing, house cleaning). The usual benefits of exercise are modest increases in lower extremity strength, endurance, and maximum O_2 consumption.

Patients should be taught ways to conserve energy during activities of daily living and to pace their activities. Difficulties in sexual function should be discussed and advice should be given on using energy-conserving techniques for sexual gratification.

Surgery:

Surgical options for treatment of severe COPD include lung volume reduction and transplantation.

Lung volume reduction surgery consists of resecting nonfunctioning emphysematous areas. The procedure improves lung function, exercise tolerance, and quality of life in patients with severe, predominantly upper-lung emphysema who have low baseline exercise capacity after pulmonary rehabilitation. Mortality is increased in the first 90 days after lung volume reduction surgery, but survival is higher at 5 yr. The effect on ABGs is variable and not predictable, but most patients who require O_2before surgery continue to need it. Improvement is less than that with lung transplantation. The mechanism of improvement is believed to be enhanced lung recoil and improved diaphragmatic function. Operative mortality is about 5%. The best candidates for lung volume reduction surgery are patients with an FEV_1 20 to 40% of predicted, a DL_{CO}> 20% of predicted, significantly impaired exercise capacity, heterogeneous pulmonary disease on CT with an upper-lobe predominance, $PaCO_2$<50 mm Hg, and absence of severe pulmonary hypertension and coronary artery disease.

Rarely, patients have extremely large bullae that compress the functional lung. These patients can be helped by surgical resection of these bullae, with resulting relief of symptoms and improved pulmonary function. Generally, resection is most beneficial for patients with bullae affecting more than one third of a hemithorax and an FEV_1 about half of the predicted normal value. Improved pulmonary function is related to the amount of normal or minimally diseased lung tissue that was compressed by the resected bullae. Serial chest x-rays and CT scans are the most useful procedures for determining whether a patient's functional status is due to compression of viable lung by bullae or to generalized emphysema. A markedly reduced DL_{CO} (< 40% predicted) indicates widespread emphysema and suggests a poorer outcome from surgical resection.

Lung transplantation can be single or double. Perioperative complications tend to be lower with single-lung transplantation, but some evidence shows that survival time is increased with double-lung transplantation. Candidates for transplantation are patients < 65 yr with an FEV_1< 25% predicted after bronchodilator therapy or with severe pulmonary hypertension. The goal of lung transplantation is to improve quality of life, because survival time is not necessarily increased. The 5-yr survival after transplantation for emphysema is 45 to 60%. Lifelong immunosuppression is required, with the attendant risk of opportunistic infections.

Treatment of Acute COPD Exacerbation

- O_2 supplementation
- Bronchodilators
- Corticosteroids
- Antibiotics
- Sometimes ventilatory assistance

The immediate objectives are to ensure adequate oxygenation and near-normal blood pH, reverse airway obstruction, and treat any cause.

The cause of an acute exacerbation is usually unknown, although some acute exacerbations result from bacterial or viral infections. Smoking, irritative inhalational exposure, and high levels of air pollution also contribute. Mild exacerbations often can be treated on an outpatient basis in patients with adequate home support. Elderly, frail patients and patients with comorbidities, a history of respiratory failure, or acute changes in ABG measurements are admitted to the hospital for observation and treatment. Patients with life-threatening exacerbations manifested by uncorrected moderate to severe acute hypoxemia, acute respiratory acidosis, new arrhythmias, or deteriorating respiratory function despite hospital treatment should be admitted to the ICU and their respiratory status monitored frequently.

O_2:

Most patients require O_2 supplementation, even those who do not need it chronically. Hypercapnia may worsen in patients given O_2. This worsening has traditionally been thought to result from an attenuation of hypoxic respiratory drive. However, increased V/Q mismatch probably is a more important factor. Before O_2 administration, pulmonary vasoconstriction minimizes V/Q mismatch by decreasing perfusion of the most poorly ventilated areas of the lungs. Increased V/Q mismatch occurs because O_2 administration attenuates this hypoxic pulmonary vasoconstriction. The Haldane effect may also contribute to worsening hypercapnia, although this theory is controversial. The Haldane effect is a decrease in Hb's affinity for CO_2, which results in increased amounts of CO_2 dissolved in plasma. O_2administration, even though it may worsen hypercapnia, is recommended; many patients with COPD have chronic as well as acute hypercapnia and thus severe CNS depression is unlikely unless $Pa_{CO_2}$is > 85 mm Hg. The target level for Pa_{O_2} is about 60 mm Hg; higher levels offer little advantage and increase the risk of hypercapnia. O_2 is given via Venturi mask so it can be closely regulated, and the patient is closely monitored. Patients whose condition deteriorates with O_2 therapy (eg, those with severe acidemia or CNS depression) require ventilatory assistance.

Many patients who require home O_2 for the first time when they are discharged from the hospital after an exacerbation improve within 30 days and no longer require O_2. Thus, the need for home O_2 should be reassessed 60 to 90 days after discharge.

Ventilatory assistance:

Noninvasive positive-pressure ventilation (eg, pressure support or bilevel positive airway pressure ventilation by face mask is an alternative to full mechanical ventilation. Noninvasive ventilation appears to decrease the need for intubation, reduce hospital stay, and reduce mortality in patients with severe exacerbations (defined as a pH < 7.30 in hemodynamically stable patients not at immediate risk of respiratory arrest). Noninvasive ventilation appears to have no effect in patients with less severe exacerbation. However, it may be indicated for patients with less severe exacerbations whose ABGs worsen despite initial drug or O_2 therapy or who appear to be imminent candidates for full mechanical ventilation but who do not require intubation for control of the airway or sedation for agitation. Patients who have severe dyspnea, hyperinflation, and use of accessory muscles of respiration may also gain relief from positive airway pressure. Deterioration while receiving noninvasive ventilation necessitates invasive mechanical ventilation.

Deteriorating ABG values and mental status and progressive respiratory fatigue are indications for endotracheal intubation and mechanical ventilation. Ventilator settings, management strategies, and complications are discussed elsewhere. Risk factors for ventilatory dependence include an

FEV_1 < 0.5 L, stable ABGs with a PaO_2 < 50 mm Hg, or a $PaCO_2$ > 60 mm Hg, severe exercise limitation, and poor nutritional status. Therefore, if patients are at high risk, discussion of their wishes regarding intubation and mechanical ventilation should be initiated and documented while they are stable outpatients. However, overconcern about possible ventilator dependence should not delay management of acute respiratory failure; many patients who require mechanical ventilation can return to their pre-exacerbation level of health.

In patients who require prolonged intubation (eg, > 2 wk), a tracheostomy is indicated to facilitate comfort, communication, and eating. With a good multidisciplinary rehabilitation program, including nutritional and psychologic support, many patients who require prolonged mechanical ventilation can be successfully liberated and can return to their former level of function. Specialized programs are available for patients who remain ventilator-dependent after acute respiratory failure. Some patients can remain off the ventilator during the day. For patients with adequate home support, training of family members can permit some patients to be sent home with ventilators.

Drug therapy:

β-Agonists and anticholinergics, with or without corticosteroids, should be started concurrently with O_2 therapy (regardless of how O_2 is administered) with the aim of reversing airway obstruction. Methylxanthines, once considered essential to treatment of acute COPD exacerbations, are no longer used; toxicities exceed benefits.

Short-acting β-agonists are the cornerstone of drug therapy for acute exacerbations. The most widely used drug is albuterol 2.5 mg by nebulizer or 2 to 4 puffs (100 mcg/puff) by metered-dose inhaler q 2 to 6 h. Inhalation using a metered-dose inhaler causes rapid bronchodilation; there are no data indicating that doses taken with nebulizers are more effective than the same doses correctly taken with metered-dose inhalers. In life-threatening exacerbations, risks of the exacerbation usually exceed those of high-dose β-agonists; thus, β-agonists may be given continuously via nebulizer until improvement occurs.

Ipratropium, an anticholinergic, is effective in acute COPD exacerbations and should be given concurrently or alternating with β-agonists. Dosage is 0.25 to 0.5 mg by nebulizer or 2 to 4 inhalations (17 to 18 mcg of drug delivered per puff) by metered-dose inhaler q 4 to 6 h. Ipratropium generally provides bronchodilating effect similar to that of usual recommended doses of β-agonists. The role of the longer-acting anticholinergic tiotropium in treating acute exacerbations has not been defined.

Corticosteroids should be begun immediately for all but mild exacerbations. Options includeprednisone 30 to 60 mg po once/day for 5 days or tapered over 7 to 14 days or methylprednisolone 60 to 500 mg IV once/day for 3 days and then tapered over 7 to 14 days. Alternatively, a 5-day course of 40 mg of prednisone appears to be equally effective. These drugs are equivalent in their acute effects; inhaled corticosteroids have no role in the treatment of acute exacerbations.

Antibiotics are recommended for exacerbations in patients with purulent sputum. Some physicians give antibiotics empirically for change in sputum color or for nonspecific chest x-ray abnormalities. Routine cultures and Gram stains are not necessary before treatment unless an unusual or resistant organism is suspected (eg, in hospitalized, institutionalized, or immunosuppressed patients). Drugs directed against oral flora are indicated. Trimethoprim /sulfamethoxazole 160 mg/800 mg po bid, amoxicillin 250 to 500 mg po tid, tetracycline 250 mg po qid, and doxycycline 50 to 100 mg po bid given for 7 to 14 days are all effective and inexpensive. Choice of drug is dictated by local patterns of bacterial sensitivity and patient history. If the patient is seriously ill or if clinical evidence suggests that the infectious organisms are resistant, broader spectrum 2nd-line drugs can be used. These drugs include amoxicillin /clavulanate 250 to 500 mg po tid, fluoroquinolones (eg, ciprofloxacin, levofloxacin), 2nd-generation cephalosporins (eg, cefuroxime, cefaclor), and extended-spectrum macrolides (eg, azithromycin, clarithromycin). These drugs are effective against β-lactamase–producing strains of H. influenzae and M. catarrhalis but have not been shown to be more effective than first-line drugs for most patients. Patients can be taught to recognize a change in sputum from normal to

purulent as a sign of impending exacerbation and to start a 10- to 14-day course of antibiotic therapy. Long-term antibiotic prophylaxis is recommended only for patients with underlying structural changes in the lung, such as bronchiectasis or infected bullae. In patients with frequent exacerbations, long-term macrolide use reduces exacerbation frequency but may have adverse effects.

Antitussives, such as dextromethorphan and benzonatate, have little role.

Opioids (eg, codein, hydrocodone, oxycodone) should be used judiciously for relief of symptoms (eg, severe coughing paroxysms, pain) insofar as these drugs may suppress a productive cough, impair mental status, and cause constipation.

End-of-life care:

With very severe disease, particularly when death is imminent, exercise is unwarranted and activities of daily living are arranged to minimize energy expenditure. For example, patients may arrange to live on one floor of the house, have several small meals rather than fewer large meals, and avoid wearing shoes that must be tied. End-of-life care should be discussed, including whether to pursue mechanical ventilation, the use of palliative sedation, and appointment of a surrogate medical decision-maker in the event of the patient's incapacitation.

Equipment: class room, Harvey cardiopulmonary patient simulator, 6-channel ECG machine CARDIOLINE 100 L and Cardioline 200 + II S.

Lesson time: 2 hours

Plan

I. Organization moments (Greeting, head count, theme announce, aim of lesson, motivating applicants to study the topic).

II. Control of basic knowledges (The task source for self-knowledge skills tests from «KROK2» - additional materials, cheking workbooks)

II.1 Requirements for theoretical readiness of applicants to perform practical classes.

Requirements to knowledges:

- Definition of chronic obstructive pulmonary disease
- Modern aspects of etiology and pathophysiology of chronic obstructive pulmonary disease
- Classification of chronic obstructive pulmonary disease
- Clinical manifestation of chronic obstructive pulmonary disease
- Laboratory and instrumental investigation of chronic obstructive pulmonary disease
- Carry out differential diagnosis of chronic obstructive pulmonary disease
- Complications of chronic obstructive pulmonary disease Treatment, rehabilitation of patients with chronic obstructive pulmonary disease
- Prognosis and disability of patients with chronic obstructive pulmonary disease

list of didactic units

- To get a detailed anamnesis
- To do physical examination of patient, to diagnose and to estimate changes in condition
- To make a plan of additional investigation and estimate it
- Justify and make a preliminary and clinical diagnoses of chronic obstructive pulmonary disease based on severity of airflow limitation, complex evaluation of chronic obstructive pulmonary disease and make a group of patients.
- Basic principles of treatment stable chronic obstructive pulmonary disease
- Estimation of exacerbation of chronic obstructive pulmonary disease and its treatment
- Estimation of clinical examination, CBC, blood tests, sputum tests, spirometry, chest X-Ray and etc.

II.2 Questions (MSQ, clinical cases) for basic knowledge examination of topic

1. What is the leading clinical symptom of COPD?
A. Cough with sputum.
B. Dyspnea. +
C. Hoarse voice.
D. Paroxysmal dry cough.
E. Pain in chest.
2. A 52 y.o. hard smoker complains of persistent cough with purulent sputum discharge especially in the mornings, dyspnea provoked even by slight physical exercises, wheezing chest, tachypnoe, general weakness. He considers himself to be ill for 12 years. The foresaid presentations appear 3-4 times per year usually after a common cold and have tendency to progress. What disease do you think about first of all?
A. Chronic obstructive lung disease.+
B. Mucoviscidosis (cystic fibrosis).
C. Bronchial asthma.
D. Bronchoectatic disease.
E. Aspergillosis.
3. A 54 y.o. male patient suffers from dyspnea during mild physical exertion, cough with sputum which is excreted with difficulty. On examination: diffuse cyanosis. Is Barrel-chest. Weakened vesicular breathing with prolonged expiration and dry whistling rales. AP is 140/80 mm Hg, pulse is 92 bpm, rhythmic. Spirography: vital capacity (VC)/predicted vital capacity- 65%, FEV1/FVC– 50%. Determine the type of respiratory insufficiency (RI).
A. RI of restrictive type.
B. RI of obstructive type. +
C. RI of mixed type with prevailing obstruction.
D. RI of mixed type with prevailing restriction.
E. There is no RI.
4. A patient 63 y.old, complains of cough with sputum, distant rales, rise of temperature to 37,5C, dyspnea at rest, increasing at a load. Illness duration 20 years. Had 3 exacerbation within the last year. Lip cyanosis, acrocyanosis. Percussion: light box sound above lungs, auscultation – disseminated dry rales on the background of a weakened vesicular respiration. Borders of a relative dullness of heart are 1,5 cm. to the right from a right edge of sternum, upper – III, intercostal space, left is 1 cm. to the left from a left midclavicular line. Heart activity is quickened, pulse 104. Accent of II tone on a pulmonary artery. Liver +2 cm. Mild swelling of ankles. Choose the probable diagnosis:
A. COPD, group B, exacerbation. LF II.
B. COPD, group C, exacerbation. LF III .
C. COPD, group D, exacerbation. LF III. Chronic cor pulmonale, HF IIA. +
D. Pulmonary emphysema. LF III. Chronic cor pulmonale, LF II.
E. Bronchial asthma IV, severe persistent course. Pulmonary emphysema. LF III.
5. A patient 55 y.old, during 7 years complains of dyspnea with insignificant amount of purulent sputum. Such symptoms are noticed in autumn and spring time. Smokes for 25 years. Temperature – 37,1°C. Lungs: weakened vesicular breathing with dry whistling rales. Chest X-ray: increased transparency of lungs, intensified lung pattern. Bronchoscopy: hyperemia of a mucous membrane with bronchial secretion of a purulent-mucous character. What's preliminary diagnosis?
A. Multiple bronchiectasis.
B. Bronchial asthma.
C. Chronic bronchitis.
D. Chronic obstructive pulmonary disease. +
E. Pneumonia.
6. During 8 years a patient is disturbed by a morning cough with little mucous sputum, dyspnea at a moderate physical exertion. Smoking duration: 20 years, 20 cigarettes a day. During examination:

moderate cyanosis, increase of duration of an expiration phase, disseminated dry rales on the background of a weakened vesicular breathing. What's the most probable diagnosis?
A. Pulmonary emphysema.
B. Chronic bronchitis.
C. Chronic obstructive pulmonary disease. +
D. Multiple bronchiectasis.
E. Bronchial asthma.
7. A patient 65 y.old, complains of expiratory dyspnea at mild exertion, underproductive cough, general weakness. Illness duration – 18 years. Disease exacerbated 2 times per last year. Smokes for 35 years. Lip cyanosis, puffy face, box-like chest, box percussion sound, coarse respiration, in inferior parts – weakened vesicular breathing, disseminated dry whistling rales, tachycardia, liver +3 cm. blood – erythrocytes $6,2x10^{12}$/l, Hb –170 g/l, ESR – 4 mm/h. Chest X-ray: lung fields of an increased transparency, lung pattern is intensified, lung roots are dilated, hypertrophy of a right ventricle. FEV1 – 38%, Tiffno index – 63%. Probable diagnosis:
A. Primary pulmonary emphysema.
B. COPD, group D +
C. COPD, group C.
D. COPD group B.
E. COPD group A.
8. A woman 52 y.old, complains of cough with purulent-mucous sputum to 30 ml a day, weakness, hyperhidrosis. Temperature – 37, 6°C, RR – 24/ min, HR 100 bpm, BP – 120/70 mmHg. During auscultation of lungs there's harsh breathing with disseminated dry and diversiform moist rales. Chest X-ray: dilation of lung roots, intensification of a lung pattern. What class of antibiotics should be preferred the treatment of a patient?
A. Macrolids. +
B. Cephalosporin of 1 generation.
C. Aminoglycosides.
D. Lincosamides.
E. Tetracycline.
9. A man 59 y.old, long-distance truck driver, complains of dyspnea at physical load, cough with little mucous sputum, mainly in the morning. A patient has been continuously having a chronic obstructive pulmonary disease, maxillary sinusitis. Smokes, smoking index 30 packs/years. Objectively: temperature – $36,5^0$C, RR – 24 /min, HR – 90 bpm, A\BP – 120/80 mmHg. During auscultation – coarse respiration, moderate quantity of dry whistling rales. FEV1 – 68%. What preventive measures are rational to be done in the first place for the prevention of a disease progress?
A. Sanation of chronic foci of infection.
B. Alcohol cessation.
C. Smoking cessation. +
E. Rational job placement.
D. Moving to another climatic zone.
10. A man 64 y.old, complains of dyspnea, which increases with a physical load. Objectively: RR – 24/min., HR – 90 bpm, BP – 125/80 mmHg, SpO2 – 87% «warm» cyanosis, swelling of neck veins, edema of lower extremities. Above lungs: weakened vesicular breathing, disseminated dry riles. Heart tones are weakened, on a pulmonary artery and to the right by the edge of sternum – systolic murmur. Liver + 5 cm. Ascites is found. ECG: RV_1 = 10 mm, SV_6 = 11 mm. What complication of a main disease can one think of?
A. Heart disease.
B. Liver cirrhosis.
C. Left-ventricular failure.
D. Chronic cor pulmonale. +
E. Asthmatic status.

III. Proffesional skills formation (skills of patient`s management, treatment)
Professional algorithms: work with a patient (according to patients-applicants conversation algorithm).

During examination students must use next algorithm:

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Collecting data on patient complains, medical history, life history
5. Interpretation of clinical, laboratory and instrumental studies
6. Explanation for patient of next acting (hospitalization, workup)
7. End of conversation

Physical examination of patient with internal diseases

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Explanation of investigations are needed, taking agreement
5. Telling about possible negative feelings during investigation
6. Preparing to examination (clean warm hands, accurate nails, warm phonendoscope, screen if needed)
7. Examination (demonstration of clinical skills)
8. Interpretation of clinical, laboratory and instrumental studies
9. End of conversation

Telling to patient with internal diseases investigation results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of investigation results
5. Conversation with patient (comparing new and previous examination results, check if explanation is clear)
6. End of conversation

Planning and prognosing treatment results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of treatment
5. Conversation with patient (explanation of features taking pills, duration of taking drugs, possible side effects)
6. Check if explanation is clear
7. End of conversation

Telling treatment prognosis

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of expected treatment results
5. Conversation with patient (explanation of importance of life-long treatment, taking medications according to list, check if explanation is clear)
6. End of conversation

Task 1

1. Collecting complains, anamnesis, examination of patients with bronchial asthma
2. Identify clinical and instrumental symptoms
3. Make a syndrome based on symptoms
4. Identify the leading clinical syndrome
5. Assign laboratory and instrumental examination (CBC, urine analysis, blood tests, sputum tests, spirometry, bronchodilatation test, chest X-Ray, ECG, EchoCG and others)
6. Carry out differential diagnosis with bronchial asthma, pneumonia
7. Make a clinical diagnosis
8. Determine a degree of disability

Task 2

Prescribing different variants of treatment according to guidelines

Task 3

Work in Internet, work with thematic literature in department library room.
Applicant must fill patient examination protocol (example is added).

Control materials for final part of the lesson:

The cases for self-control with standard answers.

1 A 52 y.o. man complaints of progressive shortness of breath and cough with purulent sputum for 2 days. He smokes a pack of cigarettes a day for 30 years. The temperature of 37,2 °C. Breathing weakened, with single dry whistling and wheezing rales. In blood: WBC 9 * 10^9 / L, the formula is not changed. Smear of sputum: large number of neutrophils and gram-negative diplococci. Chest X-ray: increased airiness of the lungs. What is the most likely diagnosis?
A. Bronchiectasis
B. Pulmonary embolism
C. COPD
D. Streptococcal infection
E. Bronchial asthma
2. A 68 y.o. patient complains of shortness of breath, dry cough, often in the morning, aching pain in the right upper quadrant of abdomen. COPD for 20 years. Objectively: diffuse face cyanosis, swelling of the neck veins, swelling of the legs, ascites. Systolic murmure over xiphoid process, accentuated of the 2nd tone on the pulmonary artery. ECG: right axis deviation, right ventricular hypertrophy. What is the most likely complication of COPD occurs in this patient?
A. Pleural effusion
B. Chronic pulmonary heart
C. Coronary heart disease
D. Lung cancer has spread to the liver and abdominal cavity
E. Exudative pericarditis
3. The 56 y.o. patient complains of shortness of breath with difficult exhale, productive cough in the morning for 22 years. Smokes one pack of cigarettes a day since 18 y.o. After bronchodilatator FEV1 increased on 10%. What drugs should be prescribed initially?
A. Inhaled corticosteroids (beclomethasone)
B. Mast cells stabilizers (intal, tayled)
C. Antibiotics (moxifloxacin)
D. Inhaled anticholinergics (Atrovent)
E. Inhaled sympathomimetic (berotek)
4. Male 61 y.o. complains of dyspnea that increases with exercise, constant mild productive cough. Smokes for over 40 years. Objective: temperature - 36,5ºC, RR - 24 / min., Pulse - 84 bpm, BP 125/85 mmHg. Asthenic, skin pale pink, prolonged exhalation through the serried lips, barrel chest, respiratory muscles are actively involved in act of breathing. Lung's auscultation - a small number

of dry rales. Spirography: VC - 71%, FEV1 - 45% from predicted. Over the last two years did not smoke daily and uses tiotropium bromide (spiriva) inhalation. The additional use of which treatment would be most effective in this case?
A Antihistamines
B Inhaled steroids
C Mucolytic
D Vaccinotherapy
E Low-flow oxygen therapy
5. Male 59 y.o., the driver complains of constant shortness of breath, which increases during exercise, unproductive cough, usually in the morning. Sick over 14 years. Smoking more than 40 years. Objective: temperature - 36,7ºC, RR - 22 / min., Pulse - 80 bpm, BP - 144/80 mmHg. Above the lungs: a large number of scattered rales. Changes of which spirographic index most likely confirm the bronchial obstruction in this patient?
A FEV1 (forced expiratory volume in 1 second)
B FVC (forced vital capacity)
C VC (vital capacity)
D PVT (peak velocity time)
E Tifno index (FEV1 / FVC)
6. A 57 y.o. patient suffers from lung disease for 12 years. The last 8 years concerned shortness of breath, cough with sputum yellow-green color, low-grade fever in the evening. Uses salbutamol, but without effect. Chest X-ray - increased pulmonary pattern. What is the most likely diagnosis?
A COPD
B Bronchial asthma
C Cystic fibrosis
D Pulmonary tuberculosis
E Bronchiectasis
7. A 54-year-old patient for 16 years suffers from cough with purulent sputum, dyspnea permanent nature, heaviness in the right upper quadrant, swelling of low extremities, increasing abdomen in size. Objectively: diffuse cyanosis. In the lungs: harsh breathing, different tone scattered dry rales, RR 30 / min. Cardiac sounds are muffled, accentueted 2nd sound on pulmonary artery. BP 150/90 mmHg. Liver +5 cm. ECG: sinus tachycardia, right axis deviation, signs of hypertrophy of the right atrium and right ventricle. What complication of COPD the patient has?
A Ischemic heart disease.
B Chronic pulmonary heart.
C Hypertension.
D Heart Failure II B.
E Mitral stenosis.
8. Patient 50 y.o. complaints with progressive dyspnea mixed-type, constant unproductive cough. Experience of smoking: more than 20 packs/year. Objectively: barrel chest, band box sound, weakened vesicular breathing with prolonged exhalation. Pulse 80 bpm. What will be the main spirometric index to verify the diagnosis?
A. FEV1<80%
B. Increase in FEV1 after test with bronchodilatator >12%
C. FVC<80%
D. Postdilated FEV1/FVC <0.70
E. FEV1 variability >20%
9. Patient 56 y.o., with new onset of COPD, GOLD 2? Complains with moucus expectoration, dyspnea at mild physical nexertion/ Objectively: lung's auscultation – harsh breathing with prolonged exhalation, dry whistling rales over the entire surface of the lungs. Select the most appropriate treatment strategy.
A. M-anticholinergics.
B. Inhaled steroids.

C. Antibiotics.
D. Systemic steroids.
E. Prolonged theophylline.
10. A patient 65 y.old, complains of expiratory dyspnea at mild exertion, underproductive cough, general weakness. Illness duration – 18 years. Disease exacerbated 2 times per last year. Smokes for 35 years. Lip cyanosis, puffy face, box-like chest, box percussion sound, coarse respiration, in inferior parts – weakened vesicular breathing, disseminated dry whistling rales, tachycardia, liver +3 cm. blood – erythrocytes $6,2x10^{12}$/l, Hb –170 g/l, ESR – 4 mm/h. Chest X-ray: lung fields of an increased transparency, lung pattern is intensified, lung roots are dilated, hypertrophy of a right ventricle. FEV1 – 38%, Tiffno index – 63%. Probable diagnosis:
A. Primary pulmonary emphysema.
B. COPD, group C.
C. COPD, group D
D. COPD group B.
E. COPD group A.
Standard answers: 1-C, 2-B, 3-D, 4-B, 5-A, 6-A, 7-B, 8-D, 9-A, 10-C.

IV. Making conclusions, telling final marks, tasks for the next lesson

Literature list
- 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 goldcopd.org/wp.../11/wms-At-A-Glance-2022-FINAL.pdf
3. BMJ Best Practice. COPD. - BMJ publishing group LTD, 2019. – 92 p.

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European male of 58 years old.
Complaints: shortness of breath for the past four days.
Medical history: He has been having intermittent chronic cough for the past 3 years. The cough is productive at times. The sputum produced is mucoid in nature and about one tablespoonful in amount. There is no blood in the sputum. It is also not foul-smelling. Patient is proceeded to have shortness of breath for the past one year. The dyspnea is persistently present and described as requiring increased effort to breathe. It is worse on exertion and patient experiences reduced effort tolerance. He is now able to climb one and a half flights of stairs before becoming breathless. He has not consulted any doctors for these symptoms prior to admission.
Life history: Material and living conditions are satisfactory. Tuberculosis, venereal disease denies. No any allergic reaction to the medications. There were no occupational hazards. Hereditary history is not burdened. Patient is a chronic smoker for the past 40 years who has been smoking about twenty sticks of cigarettes a day, does not abuse alcohol. He has not left the country for the last 3 years.
Physical examination: well nourished and alert but was tachypneic. He was able to speak in sentences but there was use of his accessory muscles. There was no clubbing or cyanosis seen. There was also no peripheral oedema, pallor or jaundice.
Vital signs: Pulse rate: 72 beats per minute, regular with good volume. No bounding pulse. RR: 28 breaths per minute. BP: 129/73 mm Hg. Temperature: 37 ℃. SpO2: 88%. On inspection of the hands, there was no peripheral cyanosis or flapping tremors seen. There was also no clubbing, muscle wasting or palmar erythema seen. There was presence of nicotine stains. On inspection of

the chest, there is an increased anterior posterior diameter giving rise to a barrel shaped chest. The chest moves equally with respiration and there is use of accessory muscles with intercostal, subcostal and suprasternal retraction. There are no chest wall deformities. On palpation, chest expansion is reduced on both sides. Tactile fremitus is equal on both sides. On percussion, there is hyperresonance over both lungs with loss of liver and cardiac dullness. On auscultation vesicular breathing is heard. There is generalised expiratory rhonchi. There is also fine early inspiratory crepitations heard at the lower zones of both lungs. The apex beat could not be palpated. There were no parasternal heaves or thrills palpable. On auscultation, normal first and second heart sounds were heard. There was mild bilateral pitting oedema. Examination of the abdomen:

On inspection, the abdomen is flat and moves with respiration. There was no guarding or tenderness. The liver and spleen were not palpable. There was no organomegaly. Examination of the neurological system was normal.

Diagnosis: Acute exacerbation of newly diagnosed chronic obstructive airway disease due to upper respiratory tract infection.

Plan of investigation:

1) Full Blood Count

Justification: In order to view the total white count as well as the differential count to see if there is an infection which has caused this episode of exacerbation. There may also be secondary polycythemia if the patient has chronic pulmonary hypertension.

Results:

White cell count : 7.91 X 109/L
Red blood cell : 4.48 X 1012/L
Haemoglobin : 133.00 g/dl
Haematocrit : 42.00 ratio
Mean cell volume : 93.80 fL
Mean cell haemoglobin : 29.70 pg
Mean cell haemoglobin conc. : 317.00 g/l
Platelets : 141.00 X 109/L
Differential count
Neutrophils : 60.10% 4.76 X 109/L
Lymphocytes : 25.30% 2.00 X 109/L
Monocytes : 13.80% 1.09 X 109/L
Eosinophils : 0.50% 0.04 X 109/L
Basophils : 0.30% 0.02 X 109/L

Interpretation: This is a normal full blood count result with normal total white count as well as normal haemoglobin levels.

2) Plain chest radiograph

Justification: Done in order to look for evidence of chronic obstructive airway disease such as hyperinflated chest or evidence of congestive cardiac failure such as cardiomegaly and prominent upper lobe vessels.

Results: Hyperinflation of the chest with the 7th anterior rib crossing the diaphragm. No other abnormalities seen.

Interpretation: Hyperinflation of the lung fields is consistent with the provisional diagnosis of chronic obstructive airway disease.

3) Sputum FEME, culture and sensitivity (not done)

Justification: In order to look for any bacteria which may have been the cause of the exacerbation . If there any organism cultured, proper antibiotics can be given based on the sensitivity test.

4) Blood urea serum electrolytes and creatinine

Justification: To look for renal impairment which may be present due to Mr TLT having hypertension. Renal impairment may also affect the dosage and type of antibiotics used.

Results:

Urea : 3.7mmol/L

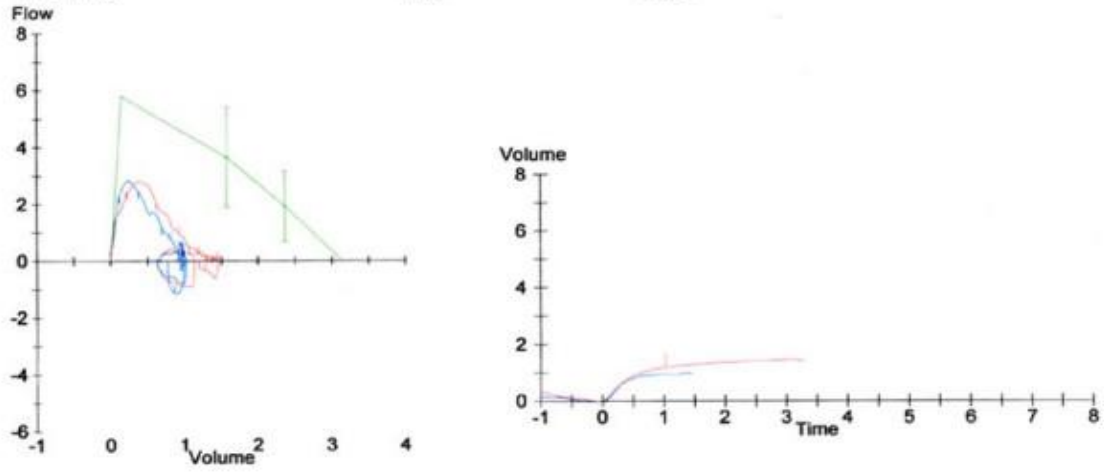
Sodium : 135 mmol/L
Potassium : 3.7 mmol/L
Creatinine : 65 umol/L
Interpretation: Normal result. There is no renal impairment

5) Electrocardiogram

Justification: To look for evidence of right ventricular hypertrophy or right atrial hypertrophy which may be seen in chronic lung disease.
Results: ECG with sinus rhythm. There is no P pulmonale seen. There is low voltage seen. No ischaemic changes seen. No left ventricular hypertrophy.
Interpretation: Normal ECG with low voltage is seen in a hyperinflated chest such as in patients with COPD

6) Spirometry

Spirometri		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	3.16	1.01	32	1.47	47	46
FEV1	Liters	3.01	0.96	32	1.21	40	26
FEV1/FVC	%	86	95		82		
FEF25%	L/min		162		158		-2
FEF50%	L/min	220	134	61	112	51	-16
FEF75%	L/min	117	62	53	30	26	-51
FEF25-75%	L/min	204	108	53	79	39	-27
PEF	L/min	349	172	49	171	49	-1
FIVC	Liters	3.16	0.23	7	0.27	8	17
FVL Time			12:17		12:39		



Diagnosis: COPD, group C, chronic pulmonary insufficiency

Acute management

1. Provide supplemental oxygen via nasal prong 3L/min and maintain SpO2 above 90%. Arterial blood gas should be done in order to ensure adequate oxygenation without carbon dioxide retention of acidosis.
2. Close monitoring of vital signs and SpO2 hourly until the patient's breathlessness improves. Nursing staff to inform if patient deteriorates such as increased respiratory rate or drop in oxygen saturation below 92%.
3. Give nebulization of Ipratropium Bromide:Salbutamol:Normal Saline in ratio of 2:2:1 every four hours until breathlessness decreases.
4. Oral prednisolone 40mg once daily for 10 days
5. Postural drainage and chest physiotherapy may be performed.

Long term management

1. Salmeterol 50 mcg in inhaler
2. Flutikazon 500 mcg in inhaler
3. Counseling on proper inhaler technique.
4. Counseling on smoking cessation.

Practical lesson № 13

Theme: Bronchial asthma

Object: To teach applicants to master the method of examination of patients with respiratory diseases with the selection of the main pulmonological syndromes. To study probable etiological factors, pathogenesis of chronic obstructive pulmonary diseases, their main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis and efficiency of patients.

Basic concepts

№	Term	Definition
1	Emphysema	destruction of the gas-exchanging surfaces of the lung (alveoli).
2	Chronic bronchitis	the presence of cough and sputum production for at least 3 months in each of two consecutive years.
3	Spirometry	is the most common of the pulmonary function tests (PFTs). Measure the volume of air forcibly exhaled from the point of maximal inspiration (forced vital capacity, FVC) and the volume of air exhaled during the first second of this maneuver (forced expiratory volume in one second, FEV1), and the ratio of these two measurements (FEV1/FVC) should be calculated.
4	Tiffeneau-Pinelli index	The FEV1/FVC ratio, used in the diagnosis of obstructive and restrictive lung disease. The diagnosis of airway obstruction is made when the FEV1/FVC ratio is less than 0.7
5	Broncho-obstructive syndrome	is a pathological condition with airflow limitation during breathing. Airway obstruction consists of reversible and irreversible components.
6	SABA	Short-acting B2-agonists - medications that relax airway smooth muscle by stimulating beta2- adrenergic receptors, works for 4-6 hours
7	LABA	Long-acting B2-agonists - medications that relax airway smooth muscle by stimulating beta2- adrenergic receptors, works for 12 or more hours
8	SAMA	Short-acting muscarinic antagonists - medications block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle
9	LAMA	Long-acting muscarinic antagonists - medications block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle, with prolonged duration of bronchodilator effect

Asthma is a disease of diffuse airway inflammation caused by a variety of triggering stimuli resulting in partially or completely reversible bronchoconstriction.

Etiology

Development of asthma is multifactorial and depends on the interactions among multiple susceptibility genes and environmental factors.

Susceptibility genes are thought to include those for T-helper cells types 1 and 2 (T_H1 and T_H2), IgE, interleukins (IL-3, -4, -5, -9, -13), granulocyte-monocyte colony-stimulating factor (GM-CSF),

tumor necrosis factor-α (TNF-α), and the *ADAM33* gene, which may stimulate airway smooth muscle and fibroblast proliferation or regulate cytokine production.

Environmental factors may include the following:

- Allergen exposure
- Diet
- Perinatal factors

Evidence clearly implicates household allergens (eg, dust mite, cockroach, pet) and other environmental allergens in disease development in older children and adults. Diets low in vitamins C and E and in ω–3 fatty acids have been linked to asthma, as has obesity. Asthma has also been linked to perinatal factors, such as young maternal age, poor maternal nutrition, prematurity, low birthweight, and lack of breastfeeding.

On the other hand, endotoxin exposure early in life can induce tolerance and may be protective. Air pollution is not definitively linked to disease development, although it may trigger exacerbations. The role of childhood exposure to cigarette smoke is controversial, with some studies finding a contributory and some a protective effect.

Genetic and environmental components may interact by determining the balance between T_H1 and T_H2 cell lineages. Infants may be born with a predisposition toward proallergic and proinflammatory T_H2 immune responses, characterized by growth and activation of eosinophils and IgE production. Early childhood exposure to bacterial and viral infections and endotoxins may shift the body to T_H1 responses, which suppresses T_H2 cells and induces tolerance. Trends in developed countries toward smaller families with fewer children, cleaner indoor environments, and early use of vaccinations and antibiotics may deprive children of these T_H2-suppressing, tolerance-inducing exposures and may partly explain the continuous increase in asthma prevalence in developed countries (the hygiene hypothesis).

Reactive airways dysfunction syndrome (RADS):

Indoor exposures to nitrogen oxide and volatile organic compounds (eg, from paints, solvents, adhesives)) are implicated in the development of RADS, a persistent asthma-like syndrome in people with no history of asthma. RADS appears to be distinct from asthma and may be, on occasion, a form of environmental lung disease. However, RADS and asthma have many clinical similarities (eg, wheezing, dyspnea, cough), and both may respond to corticosteroids.

Pathophysiology

Asthma involves

- Bronchoconstriction
- Airway edema and inflammation
- Airway hyperreactivity
- Airway remodeling

In patients with asthma, T_H2 cells and other cell types—notably, eosinophils and mast cells, but also other CD4+ subtypes and neutrophils—form an extensive inflammatory infiltrate in the airway epithelium and smooth muscle, leading to airway remodeling (ie, desquamation, subepithelial fibrosis, angiogenesis, smooth muscle hypertrophy). Hypertrophy of smooth muscle narrows the airways and increases reactivity to allergens, infections, irritants, parasympathetic stimulation (which causes release of pro-inflammatory neuropeptides, such as substance P, neurokinin A, and calcitonin gene-related peptide), and other triggers of bronchoconstriction. Additional contributors to airway hyperreactivity include loss of inhibitors of bronchoconstriction (epithelium-derived relaxing factor, prostaglandin E_2) and loss of other substances called endopeptidases that metabolize endogenous bronchoconstrictors. Mucus plugging and peripheral blood eosinophilia are additional classic findings in asthma and may be epiphenomena of airway inflammation. However, not all patients with asthma have eosinophilia.

Triggers:

Common triggers of an asthma exacerbation include

- Environmental and occupational allergens (numerous)
- Infections

- Exercise
- Inhaled irritants
- Emotion
- Aspirin
- Gastroesophageal reflux disease (GERD)

Infectious triggers in young children include respiratory syncytial virus, rhinovirus, and parainfluenza virus infection. In older children and adults, URIs (particularly with rhinovirus) and pneumonia are common infectious triggers. Exercise can be a trigger, especially in cold or dry environments. Inhaled irritants, such as air pollution, cigarette smoke, perfumes, and cleaning products, are often involved. Emotions such as anxiety, anger, and excitement sometimes trigger exacerbations.

Aspirin is a trigger in up to 30% of older patients and in patients with more severe asthma. Aspirin-induced asthma is typically accompanied by nasal polyps with nasal and sinus congestion.

GERD is a common trigger among some patients with asthma, possibly via esophageal acid-induced reflex bronchoconstriction or by microaspiration of acid. However, treatment of asymptomatic GERD (eg, with proton pump inhibitors) does not seem to improve asthma control.

Allergic rhinitis often coexists with asthma; it is unclear whether the two are different manifestations of the same allergic process or whether rhinitis is a discrete asthma trigger.

Response:

In the presence of triggers, there is reversible airway narrowing and uneven lung ventilation. Relative perfusion exceeds relative ventilation in lung regions distal to narrowed airways; thus, alveolar O_2 tensions fall and alveolar CO_2 tensions rise. Most patients can compensate by hyperventilating, but in severe exacerbations, diffuse bronchoconstriction causes severe gas trapping, and the respiratory muscles are put at a marked mechanical disadvantage so that the work of breathing increases. Under these conditions, hypoxemia worsens and $PaCO_2$ rises. Respiratory and metabolic acidosis may result and, if left untreated, cause respiratory and cardiac arrest.

Classification

Unlike hypertension, for example, in which one parameter (BP) defines the severity of the disorder and the efficacy of treatment, asthma causes a number of clinical and testing abnormalities. Also unlike most hypertension, asthma manifestations typically wax and wane. Thus, monitoring (and studying) asthma requires a consistent terminology and defined benchmarks.

Severity is the intrinsic intensity of the disease process (ie, how bad it is). Severity can usually be assessed directly only before treatment is started, because patients who have responded well to treatment by definition have few symptoms. Asthma severity is categorized as

- Intermittent
- Mild persistent
- Moderate persistent
- Severe persistent

The term status asthmaticus describes severe, intense, prolonged bronchospasm that is resistant to treatment.

Control is the degree to which symptoms, impairments, and risks are minimized by treatment. Control is the parameter assessed in patients receiving treatment. The goal is for all patients to have well controlled asthma regardless of disease severity. Control is classified as

- Well controlled
- Not well controlled
- Very poorly controlled

Classification of Asthma Control

Component	Well-Controlled	Not Well-Controlled	Very Poorly Controlled
Symptoms	All ages except children 5–11 yr: ≤2	All ages except children 5–11 yr: >2	For all ages: Throughout the day

	days/wk Children 5–11 yr: ≤2 days/wk but not> once/day	days/wk Children 5–11 yr: >2 days/wk or multiple times on ≤ 2 days/wk	
Nighttime awakenings	Adults and children ≥ 12 yr: ≤ 2/mo Children 5–11 yr: ≤1 /mo Children 0–4 yr: ≤ 1 /mo	Adults and children ≥ 12 yr: 1–3/wk Children 5–11 yr: ≥ 2/mo Children 0–4 yr: >1/mo	Adults and children ≥ 12 yr: ≥ 4/wk Children 5–11 yr: ≥2/wk Children 0–4 yr: >1/wk
Interference with normal activity	None	Some limitation	Extreme limitation
Use of short-actingβ_2-agonist for symptom control (not prevention of exercise-induced asthma)	≤ 2 days/wk	> 2 days/wk	Several times/day
FEV_1 or peak flow	> 80% predicted/personal best	60–80% predicted/personal best	< 60% predicted/personal best
FEV_1/FVC (children 5–11 yr)	> 80%	75–80%	< 75%
Exacerbations requiring oral systemic corticosteroids‡	0–1/yr	Adults and children ≥ 5 yr: ≥ 2/yr Children 0–4 yr: 2–3/yr	Adults and children ≥ 5 yr: ≥ 2/yr Children 0–4 yr: >3/yr
Validated questionnaires:			
• ATAQ	0	1–2	3−4
• ACQ	≤ 0.75†	≥ 1.5	N/A
• ACT	≥ 20	16−19	≤ 15
Recommended action	Maintain current step Follow up every 1–6 mo Consider step down if well controlled for ≥ 3 mo	Step up 1 step Reevaluate in 2–6 wk For adverse effects, consider treatment options	Consider short course of systemic corticosteroids Step up 1 or 2 steps Reevaluate in 2 wk For adverse effects, consider treatment options

Level of control is based on the most severe impairment or risk category. Additional factors to consider are progressive loss of lung function on pulmonary function tests, significant adverse effects, and severity and interval between exacerbations (ie, one exacerbation requiring intubation or 2 hospitalizations within 1 mo may be considered very poor control).

‡At present, there are inadequate data to correlate frequencies of exacerbations with different levels of asthma control. In general, more frequent and intense exacerbations (eg, requiring urgent, unscheduled care, hospitalization, or ICU admission) indicate poorer asthma control.

ACQ = asthma control questionnaire; ACT = asthma control test; ATAQ = asthma therapy assessment questionnaire; FEV_1 = forced expiratory volume in 1 sec; FVC = forced vital capacity.

Impairment refers to the frequency and intensity of patients' symptoms and functional limitations. Impairment is assessed by spirometry, mainly forced expiratory volume in 1 sec (FEV_1), and the ratio of FEV_1 to forced vital capacity (FVC), as well as clinical features such as

- How often symptoms are experienced
- How often the patient awakens at night
- How often the patient uses a short-acting β_2-agonist for symptom relief
- How often asthma interferes with normal activity

Risk refers to the likelihood of future exacerbations or decline in lung function and the risk of adverse drug effects. Risk is assessed by long-term trends in spirometry and clinical features such as

- Frequency of need for oral corticosteroids
- Need for hospitalization
- Need for ICU admission
- Need for intubation

It is important to remember that the severity category does not predict how serious an exacerbation a patient may have. For example, a patient who has mild asthma with long periods of no or mild symptoms and normal pulmonary function may have a severe, life-threatening exacerbation.

Symptoms and Signs

Patients with mild asthma are typically asymptomatic between exacerbations. Patients with more severe disease and those with exacerbations experience dyspnea, chest tightness, audible wheezing, and coughing. Coughing may be the only symptom in some patients (cough-variant asthma). Symptoms can follow a circadian rhythm and worsen during sleep, often around 4 AM. Many patients with more severe disease waken during the night (nocturnal asthma).

Signs include wheezing, pulsus paradoxus (ie, a fall of systolic BP > 10 mm Hg during inspiration), tachypnea, tachycardia, and visible efforts to breathe (use of neck and suprasternal [accessory] muscles, upright posture, pursed lips, inability to speak). The expiratory phase of respiration is prolonged, with an inspiratory:expiratory ratio of at least 1:3. Wheezes can be present through both phases or just on expiration, but patients with severe bronchoconstriction may have no audible wheezing because of markedly limited airflow.

Patients with a severe exacerbation and impending respiratory failure typically have some combination of altered consciousness, cyanosis, pulsus paradoxus > 15 mm Hg, SaO_2< 90%, $PaCO_2$> 45 mm Hg, or hyperinflation. Rarely, pneumothorax or pneumomediastinum is seen on chest x-ray.

Symptoms and signs disappear between exacerbations, although soft wheezes may be audible during forced expiration at rest, or after exercise in some asymptomatic patients. Hyperinflation of the lungs may alter the chest wall in patients with long-standing uncontrolled asthma, causing a barrel-shaped thorax.

All symptoms and signs are nonspecific, are reversible with timely treatment, and typically are brought on by exposure to one or more triggers.

Diagnosis

- Clinical evaluation
- Pulmonary function testing

Diagnosis is based on history and physical examination and is confirmed with pulmonary function tests. Diagnosis of causes and the exclusion of other disorders that cause wheezing are also important. Asthma and COPD are sometimes easily confused; they cause similar symptoms and produce similar results on pulmonary function tests but differ in important biologic ways that are not always clinically apparent.

Pulmonary function tests:

Patients suspected of having asthma should undergo pulmonary function testing to confirm and quantify the severity and reversibility of airway obstruction. Pulmonary function data quality is effort-dependent and requires patient education before the test. If it is safe to do so, bronchodilators should be stopped before the test: 6 h for short-acting β_2-agonists, such as albuterol; 8 h

for ipratropium; 12 to 36 h for theophylline; 24 h for long-acting β_2-agonists, such as salmeterol and formoterol; and 48 h for tiotropium.

Spirometry should be done before and after inhalation of a short-acting bronchodilator. Signs of airflow limitation before bronchodilator inhalation include reduced FEV_1 and a reduced FEV_1/FVC ratio. The FVC may also be decreased because of gas trapping, such that lung volume measurements may show an increase in the residual volume, the functional residual capacity, or both. An improvement in FEV_1 of > 12% or an increase ≥ 10% of predicted FEV_1 in response to bronchodilator treatment confirms reversible airway obstruction, although absence of this finding should not preclude a therapeutic trial of bronchodilators. Spirometry should be repeated at least every 1 to 2 yr in patients with asthma to monitor disease progression.

Flow-volume loops should also be reviewed to diagnose vocal cord dysfunction, a common cause of upper airway obstruction that mimics asthma.

Provocative testing, in which inhaled methacholine (or alternatives, such as inhaled histamine,adenosine, or bradykinin, or exercise testing) is used to provoke bronchoconstriction, is indicated for patients suspected of having asthma who have normal findings on spirometry and flow-volume testing and for patients suspected of having cough-variant asthma, provided there are no contraindications. Contraindications include FEV_1< 1 L or < 50% predicted, recent MI or stroke, and severe hypertension (systolic BP > 200 mm Hg; diastolic BP > 100 mm Hg). A decline in FEV_1 of > 20% on a provocative testing protocol is relatively specific for the diagnosis of asthma. However, FEV_1 may decline in response to these drugs in other disorders, such as COPD. If FEV_1 decreases by < 20% by the end of the testing protocol, asthma is less likely to be present.

Other tests:

Other tests may be helpful in some circumstances:

- Diffusing capacity for carbon monoxide (DL_{CO})
- Chest x-ray
- Allergy testing

DL_{CO} testing can help distinguish asthma from COPD. Values are normal or elevated in asthma and usually reduced in COPD, particularly in patients with emphysema.

A chest x-ray may help exclude some causes of asthma or alternative diagnoses, such as heart failure or pneumonia. The chest x-ray in asthma is usually normal but may show hyperinflation or segmental atelectasis, a sign of mucous plugging. Infiltrates, especially those that come and go and that are associated with findings of central bronchiectasis, suggest allergic bronchopulmonary aspergillosis .

Allergy testing may be indicated for children whose history suggests allergic triggers (particularly for allergic rhinitis) because these children may benefit from immunotherapy. It should be considered for adults whose history indicates relief of symptoms with allergen avoidance and for those in whom a trial of therapeutic anti-IgE antibody therapy is being considered. Skin testing and measurement of allergen-specific IgE via radioallergosorbent testing (RAST) can identify specific allergic triggers.

Elevated blood eosinophils (> 400 cells/μL) and nonspecific IgE (> 150 IU) are suggestive but not diagnostic of allergic asthma because they can be elevated in other conditions. However, eosinophilia is not sensitive.

Sputum evaluation for eosinophils is not commonly done; finding large numbers of eosinophils is suggestive of asthma but is neither sensitive nor specific.

Peak expiratory flow (PEF) measurements with inexpensive handheld flow meters are recommended for home monitoring of disease severity and for guiding therapy.

Evaluation of exacerbations:

Patients with asthma with an acute exacerbation should have certain tests:

- Pulse oximetry
- PEF or FEV_1 measurement

All 3 measures help establish the severity of an exacerbation and document treatment response. PEF values are interpreted in light of the patient's personal best, which may vary widely among patients

who are equally well controlled. A 15 to 20% reduction from this baseline indicates a significant exacerbation. When baseline values are not known, the percent predicted FEV_1 value gives a general idea of airflow limitation but not the individual patient's degree of worsening. When measuring FEV_1 is impractical (eg, in an emergency department) and baseline PEF is unknown, percent of predicted PEF based on age, height and sex may be used. Although percent predicted PEF is less accurate than comparison to a personal best, it may be helpful as a baseline to evaluate treatment response.

Chest x-ray is not necessary for most exacerbations but should be done in patients with symptoms or signs suggestive of pneumonia, pneumothorax, or pneumomediastinum.

ABG measurements should be done in patients with marked respiratory distress or symptoms and signs of impending respiratory failure.

Prognosis

Asthma resolves in many children, but for as many as 1 in 4, wheezing persists into adulthood or relapse occurs in later years. Female sex, smoking, earlier age of onset, sensitization to household dust mites, and airway hyperresponsiveness are risk factors for persistence and relapse.

Although a significant number of deaths each year are attributable to asthma, most of these are preventable with treatment. Thus, the prognosis is good with adequate access and adherence to treatment. Risk factors for death include increasing requirements for oral corticosteroids before hospitalization, previous hospitalization for acute exacerbations, and lower PEF values at presentation. Several studies show that use of inhaled corticosteroids decreases hospital admission and mortality rates.

Over time, the airways in some patients with asthma undergo permanent structural changes (remodeling) that prevent return to normal lung functioning. Early aggressive use of anti-inflammatory drugs may help prevent this remodeling.

Treatment

- Control of triggers
- Drug therapy
- Monitoring
- Patient education
- Treatment of acute exacerbations

Treatment objectives are to minimize impairment and risk, including preventing exacerbations and minimizing chronic symptoms, including nocturnal awakenings; to minimize the need for emergency department visits or hospitalizations; to maintain baseline (normal) pulmonary function and activity levels; and to avoid adverse treatment effects.

Control of triggering factors:

Triggering factors in some patients may be controlled with use of synthetic fiber pillows and impermeable mattress covers and frequent washing of bed sheets, pillowcases, and blankets in hot water. Upholstered furniture, soft toys, carpets, and pets should be removed to reduce dust mites and animal dander. Dehumidifiers should be used in basements and in other poorly aerated, damp rooms to reduce mold. Steam treatment of homes diminishes dust mite allergens. House cleaning and extermination to eliminate cockroach exposure is especially important. Although control of triggering factors is more difficult in urban environments, the importance of these measures is not diminished. High-efficiency particulate air (HEPA) vacuums and filters may relieve symptoms, but no beneficial effects on pulmonary function and on the need for drugs have been observed. Sulfite-sensitive patients should avoid red wine. Nonallergenic triggers, such as cigarette smoke, strong odors, irritant fumes, cold temperatures, high humidity, and exercise, should also be avoided or controlled when possible. Limiting exposure to people with viral URIs is also important.

Patients with aspirin-induced asthma can use acetaminophen, choline magnesium salicylate, or celecoxib in place of NSAIDs.

Asthma is a relative contraindication to the use of nonselective β-blockers, including topical formulations, but cardioselective drugs (eg, metoprolol, atenolol) probably have no adverse effects.

Drug therapy:

Major drug classes commonly used in the treatment of chronic asthma and asthma exacerbations include

- Bronchodilators (β_2-agonists, anticholinergics)
- Corticosteroids
- Leukotriene modifiers
- Mast cell stabilizers
- Methylxanthines

Drugs in these classes are inhaled or taken orally; inhaled drugs come in aerosolized and powdered forms. Use of aerosolized forms with a spacer or holding chamber facilitates deposition of the drug in the airways rather than the pharynx; patients are advised to wash and dry their spacers after each use to prevent bacterial contamination. In addition, use of aerosolized forms requires coordination between actuation of the inhaler (drug delivery) and inhalation; powdered forms reduce the need for coordination, because drug is delivered only when the patient inhales. In addition, powdered forms reduce the release of fluorocarbon propellants into the environment.

β_2-Agonists relax bronchial smooth muscle, decrease mast cell degranulation and histamine release, inhibit microvascular leakage into the airways, and increase mucociliary clearance. β_2-Agonists come in short- and long-acting preparations. Short-acting β_2-agonists (eg, albuterol) 2 puffs q 4 h inhaled prn are the drug of choice for relieving acute bronchoconstriction and preventing exercise-induced asthma. They are not used for long-term maintenance. They take effect within minutes and are active for up to 6 to 8 h, depending on the drug. Tachycardia and tremor are the most common acute adverse effects of inhaled β_2-agonists and are dose-related. Mild hypokalemia occurs uncommonly. Use of levalbuterol (a solution containing the *R*-isomer of albuterol) theoretically minimizes adverse effects, but its long-term efficacy and safety are unproved. Oral β_2-agonists have more systemic effects and generally should be avoided.

Long-acting β_2-agonists (eg, salmeterol) are active for up to 12 h and are used for moderate and severe asthma but should never be used as monotherapy. They interact synergistically with inhaled corticosteroids and permit lower dosing of corticosteroids. The safety of regular long-term use of β_2-agonists is controversial. Long-acting β_2-agonists may increase the risk of asthma-related death. Therefore, when treating patients with asthma, salmeterol should be used only as additional therapy, not monotherapy, for patients whose condition is not adequately controlled with other asthma controllers (eg, low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants additional maintenance therapies. Daily use of β_2-agonists, increased dosing or diminishing effects, or use of ≥ 1 canisters a month suggests inadequate control and the need to begin or intensify other therapies.

Anticholinergics relax bronchial smooth muscle through competitive inhibition of muscarinic (M_3) cholinergic receptors. Ipratropium may have an additive effect when combined with short-acting β_2-agonists. Adverse effects include pupillary dilation, blurred vision, and dry mouth. Tiotropium is a 24-h inhaled anticholinergic that can be used for patients with COPD. In patients with asthma, recent clinical trials of tiotropium added to either inhaled corticosteroids or to a combination of an inhaled long-acting β_2-agonist plus a corticosteroid have shown improved pulmonary function and decreased asthma exacerbations. Data concerning the long-term safety of tiotropium in patients with asthma are incomplete.

Corticosteroids inhibit airway inflammation, reverse β-receptor down-regulation, and inhibit cytokine production and adhesion protein activation. They block the late response (but not the early response) to inhaled allergens. Routes of administration include oral, IV, and inhaled. In acute asthma exacerbations, early use of systemic corticosteroids often aborts the exacerbation, decreases the need for hospitalization, prevents relapse, and speeds recovery. Oral and IV routes are equally effective. Inhaled corticosteroids have no role in acute exacerbations but are indicated for long-term suppression, control, and reversal of inflammation and symptoms. They substantially reduce the need for maintenance oral corticosteroid therapy. Adverse local effects of inhaled corticosteroids include dysphonia and oral candidiasis, which can be prevented or minimized by having the patient

use a spacer, gargle with water after corticosteroid inhalation, or both. Systemic effects are all dose related, can occur with oral or inhaled forms, and occur mainly with inhaled doses > 800 mcg/day. They include suppression of the adrenal-pituitary axis, osteoporosis, cataracts, skin atrophy, hyperphagia, and easy bruisability. Whether inhaled corticosteroids suppress growth in children is controversial. Most children reach their predicted adult height. Latent TB may be reactivated by systemic corticosteroid use.

Mast cell stabilizers inhibit histamine release from mast cells, reduce airway hyperresponsiveness, and block the early and late responses to allergens. They are given by inhalation prophylactically to patients with exercise-induced or allergen-induced asthma. They are ineffective once symptoms have occurred. They are the safest of all antiasthmatic drugs but the least effective.

Leukotriene modifiers are taken orally and can be used for long-term control and prevention of symptoms in patients with mild persistent to severe persistent asthma. The main adverse effect is liver enzyme elevation (which occurs with zileuton). Although rare, patients have developed a clinical syndrome resembling eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome).

Methylxanthines relax bronchial smooth muscle (probably by inhibiting phosphodiesterase) and may improve myocardial and diaphragmatic contractility through unknown mechanisms. Methylxanthines appear to inhibit intracellular release of Ca, decrease microvascular leakage into the airway mucosa, and inhibit the late response to allergens. They decrease the infiltration of eosinophils into bronchial mucosa and of T cells into epithelium. The methylxanthine theophylline is used for long-term control as an adjunct to β_2-agonists. Extended-release theophylline helps manage nocturnal asthma. Theophylline is falling into disuse because of its many adverse effects and interactions compared with other drugs. Adverse effects include headache, vomiting, cardiac arrhythmias, and seizures. Methylxanthines have a narrow therapeutic index; multiple drugs (any metabolized by the cytochrome P-450 pathway, eg, macrolide antibiotics) and conditions (eg, fever, liver disease, heart failure) alter methylxanthine metabolism and elimination. Serum theophylline levels should be monitored periodically and maintained between 5 and 15 μg/mL (28 and 83 μmol/L).

Immunomodulators include omalizumab, an anti-IgE antibody developed for use in severely allergic patients with asthma who have elevated IgE levels. Omalizumab may decrease asthma exacerbations, decreases corticosteroid requirements, and relieves symptoms. Dosing is determined by a dosing chart based on the patient's weight and IgE levels. The drug is administered sc q 2 to 4 wk. Clinicians who administer omalizumab should be prepared to identify and treat anaphylaxis, which may occur after any dose of omalizumab, even if previous doses have been well tolerated.

Other drugs are used uncommonly in specific circumstances. Magnesium is often used in the emergency department, but it is not recommended in the management of chronic asthma. Immunotherapy may be indicated when symptoms are triggered by allergy, as suggested by history and confirmed by allergy testing. Immunotherapy is generally more effective in children than adults. If symptoms are not significantly relieved after 24 mo, then therapy is stopped. If symptoms are relieved, therapy should continue for ≥ 3 yr, although the optimum duration is unknown. Other drugs that suppress the immune system are occasionally given to reduce dependence on high-dose oral corticosteroids, but these drugs have a significant risk of toxicity. Low-dose methotrexate (5 to 15 mg po or IM once/wk) can lead to modest improvements in FEV_1 and modest decreases in daily oral corticosteroid use. Gold and cyclosporine are also modestly effective, but toxicity and need for monitoring limit their use. Other therapies for management of chronic asthma include nebulized lidocaine, nebulized heparin, colchicine, and high-dose IV immune globulin. Limited evidence supports the use of any of these therapies, and their benefits are unproved, so none are currently recommended for routine clinical use.

Monitoring response to treatment:

Guidelines recommend office use of spirometry (FEV_1, FEV_1/FVC, FVC) to measure airflow limitation and assess impairment and risk. Outside the office, home PEF monitoring, in conjunction with patient symptom diaries and the use of an asthma action plan, is especially useful for charting

disease progression and response to treatment in patients with moderate to severe persistent asthma. When asthma is quiescent, one PEF measurement in the morning suffices. Should PEF measurements fall to < 80% of the patient's personal best, then twice/day monitoring to assess circadian variation is useful. Circadian variation of > 20% indicates airway instability and the need to re-evaluate the therapeutic regimen.

Patient education:

The importance of patient education cannot be overemphasized. Patients do better when they know more about asthma—what triggers an exacerbation, what drug to use when, proper inhaler technique, how to use a spacer with a metered-dose inhaler (MDI), and the importance of early use of corticosteroids in exacerbations. Every patient should have a written action plan for day-to-day management, especially for management of acute exacerbations, that is based on the patient's best personal peak flow rather than on a predicted normal value. Such a plan leads to much better asthma control, largely attributable to improved adherence to therapies.

Treatment of acute exacerbation:

The goal of asthma exacerbation treatment is to relieve symptoms and return patients to their best lung function. Treatment includes

- Inhaled bronchodilators (β_2-agonists and anticholinergics)
- Usually systemic corticosteroids

Patients having an exacerbation are instructed to self-administer 2 to 4 puffs of inhaled albuterol or a similar short-acting β_2-agonist up to 3 times spaced 20 min apart for an acute exacerbation and to measure PEF if possible. When these short-acting rescue drugs are effective (symptoms are relieved and PEF returns to > 80% of baseline), the acute exacerbation may be managed in the outpatient setting. Patients who do not respond, have severe symptoms, or have a PEF persistently < 80% should follow a treatment management program outlined by the physician or should go to the emergency department.

Inhaled bronchodilators (β_2-agonists and anticholinergics) are the mainstay of asthma treatment in the emergency department. In adults and older children, albuterol given by an MDI and spacer is as effective as that given by nebulizer. Nebulized treatment is preferred for younger children because of difficulties coordinating MDIs and spacers; evidence suggests that bronchodilator response improves when the nebulizer is powered with helium-O_2 (heliox) rather than with O_2. Subcutaneous epinephrine 1:1000 solution or terbutaline is an alternative for children. Terbutaline may be preferable to epinephrine because of its lesser cardiovascular effects and longer duration of action, but it is no longer produced in large quantities and is expensive. Subcutaneous administration of β_2-agonists in adults raises concerns of adverse cardiostimulatory effects. However, clinically important adverse effects are few, and subcutaneous administration may benefit patients unresponsive to maximal inhaled therapy or patients unable to receive effective nebulized treatment (eg, those who cough excessively, have poor ventilation, or are uncooperative).

Nebulized ipratropium can be co-administered with nebulized albuterol for patients who do not respond optimally to albuterol alone; some evidence favors simultaneous high-dose β_2-agonist and ipratropium as first-line treatment, but no data favor continuous β_2-agonist nebulization over intermittent administration.

Systemic corticosteroids (prednisone, prednisolone, methylprednisolone) should be given for all but the mildest acute exacerbation; they are unnecessary for patients whose PEF normalizes after 1 or 2 bronchodilator doses. IV and oral routes of administration are probably equally effective. IV methylprednisolone can be given if an IV line is already in place and can be switched to oral dosing whenever necessary or convenient. Tapering usually starts after 7 to 10 days and should last 2 to 3 wk.

Antibiotics are indicated only when history, examination, or chest x-ray suggests underlying bacterial infection; most infections underlying asthma exacerbations are probably viral in origin.

Supplemental O_2 is indicated for hypoxemia and should be given by nasal cannula or face mask at a flow rate or concentration sufficient to maintain O_{2sat}> 90%.

Reassurance is the best approach when anxiety is the cause of asthma exacerbation. Anxiolytics and morphine are relatively contraindicated because they are associated with increased mortality and the need for mechanical ventilation.

Hospitalization generally is required if patients have not returned to their baseline within 4 h of aggressive emergency department treatment. Criteria for hospitalization vary, but definite indications are failure to improve, worsening fatigue, relapse after repeated β_2-agonist therapy, and significant decrease in Pa_{O_2} (< 50 mm Hg) or increase in Pa_{CO_2} (> 40 mm Hg), indicating progression to respiratory failure.

Patients who continue to deteriorate despite aggressive treatment are candidates for noninvasive positive pressure ventilation or endotracheal intubation and invasive mechanical ventilation. Patients requiring intubation may benefit from sedation, but routine use of neuromuscular blocking agents should be avoided because of possible interactions with corticosteroids that can cause prolonged neuromuscular weakness.

Generally, volume-cycled ventilation in assist-control mode is used because it provides constant alveolar ventilation when airway resistance is high and changing. The ventilator should be set to a relatively low frequency with a relatively high inspiratory flow rate (> 80 L/min) to prolong exhalation time, minimizing auto positive end-expiratory pressure (PEEP). Initial tidal volumes can be set to 6 to 8 mL/kg of ideal body weight. High peak airway pressures will generally be present because they result from high airway resistance and inspiratory flow rates. In these patients, peak airway pressure does not reflect the degree of lung distention caused by alveolar pressure. However, if plateau pressures exceed 30 to 35 cm H_2O, then tidal volume should be reduced to limit the risk of pneumothorax. When reduced tidal volumes are necessary, a moderate degree of hypercapnia is acceptable, but if arterial pH falls below 7.10, a slow $NaHCO_3$ infusion is indicated to maintain pH between 7.20 and 7.25. Once airflow obstruction is relieved and Pa_{CO_2} and arterial pH normalize, patients can usually be quickly weaned from the ventilator.

Other therapies are reportedly effective for asthma exacerbation, but none have been thoroughly studied. Heliox is used to decrease the work of breathing and improve ventilation through a decrease in turbulent flow attributable to helium, a gas less dense than O_2. Despite the theoretical benefits of heliox, studies have reported conflicting results concerning its efficacy; lack of ready availability and inability to concurrently provide high concentrations of O_2 (due to the fact that 70 to 80% of the inhaled gas is helium) may also limit its use. Magnesium sulfate relaxes smooth muscle, but efficacy in management of asthma exacerbation in the emergency department is debated. General anesthesia in patients with status asthmaticus causes bronchodilation by an unclear mechanism, perhaps by a direct relaxant effect on airway smooth muscle or attenuation of cholinergic tone.

Treatment of chronic asthma:

Current asthma guidelines initiate treatment based on the severity classification. Continuing therapy is based on assessment of control. Therapy is increased in a stepwise fashion until the best control of impairment and risk is achieved (step-up). Before therapy is stepped up, adherence, exposure to environmental factors (eg, trigger exposure), and presence of comorbid conditions (eg, obesity, allergic rhinitis, GERD, COPD, obstructive sleep apnea, vocal cord dysfunction) are reviewed. These factors should be addressed before increasing drug therapy. Once asthma has been well controlled for at least 3 mo, drug therapy is reduced if possible to the minimum that maintains good control (step-down).

Steps of Asthma Management

Step	Preferred Treatment	Alternate Treatment
1 (starting point for intermittent asthma)	Short-acting β_2-agonist prn[†]	—
2 (starting point for mild persistent asthma)	Low-dose inhaled corticosteroid	Mast cell stabilizer, leukotriene receptor antagonist, or theophylline

3 (starting point for moderate persistent asthma)	Medium-dose inhaled corticosteroid *or* Low-dose inhaled corticosteroid plus long-acting β_2-agonist	Low-dose inhaled corticosteroid plus one of the following: a leukotriene receptor antagonist,theophylline, or zileuton
4	Medium-dose inhaled corticosteroid plus long-acting β_2-agonist	Medium-dose inhaled corticosteroid plus one of the following: leukotriene receptor antagonist,theophylline, or zileuton
5 (starting point for severe persistent asthma)	High-dose inhaled corticosteroid plus long-acting β_2-agonist *and* possibly omalizumab for patients with allergies	—
6	High-dose inhaled corticosteroid plus long-acting β_2-agonist plus oral corticosteroid *and* possibly omalizumab for patients with allergies	—
Before stepping up, adherence, environmental factors (eg, trigger exposure), and comorbid conditions should be reviewed and managed if needed.		
†A short-acting ß$_2$-agonist is indicated to provide quick relief at all steps and to prevent exercise-induced asthma.		

Exercise-induced asthma:

Exercise-induced asthma can generally be prevented by inhalation of a short-acting β_2-agonist or mast cell stabilizer before starting the exercise. If β_2-agonists are not effective or if exercise-induced asthma is associated with severe symptoms, the patient likely has more severe asthma than was initially recognized and requires controller therapy.

Aspirin-sensitive asthma:

The primary treatment for aspirin-sensitive asthma is avoidance of NSAIDs. Celecoxib does not appear to be a trigger. Leukotriene modifiers can blunt the response to NSAIDs. Alternatively, inpatient desensitization has been successful in a few patients.

Future therapies:

Multiple therapies are being developed to target specific components of the inflammatory cascade. Therapies directed at IL-4, IL-13, tumor necrosis factor-α, other chemokines, and cytokines or their receptors are all under investigation or consideration as therapeutic targets.

Special Populations

Infants, children, and adolescents:

Asthma is difficult to diagnose in infants; thus, under-recognition and undertreatment are common. Empiric trials of inhaled bronchodilators and anti-inflammatory drugs may be helpful for both. Drugs may be given by nebulizer or MDI with a holding chamber with or without a face mask. Infants and children < 5 yr requiring treatment > 2 times/wk should be given daily anti-inflammatory therapy with inhaled corticosteroids (preferred), leukotriene receptor antagonists, orcromolyn.

Children > 5 yr and adolescents with asthma can be treated similarly to adults. They should be encouraged to maintain physical activities, exercise, and sports participation. Predicted norms for pulmonary function tests in adolescents are closer to childhood (not adult) standards. Adolescents

and mature younger children should participate in developing their own asthma management plans and establishing their own goals for therapy to improve adherence. The action plan should be understood by teachers and school nurses to ensure reliable and prompt access to rescue drugs. Cromolyn andnedocromil are often tried in this group but are not as beneficial as inhaled corticosteroids. Long-acting drugs prevent the problems (eg, inconvenience, embarrassment) of having to take drugs at school.

Pregnant women:

About one third of women with asthma who become pregnant notice relief of symptoms, one third notice worsening (at times to a severe degree), and one third notice no change. GERD may be an important contributor to symptomatic disease in pregnancy. Asthma control during pregnancy is crucial, because poorly controlled maternal disease can result in increased prenatal mortality, premature delivery, and low birth weight. Asthma drugs have not been shown to have adverse fetal effects, but safety data are lacking. In general, uncontrolled asthma is more of a risk to mother and fetus than adverse effects due to asthma drugs. During pregnancy, normal blood PCO_2 level is about 32 mm Hg. Therefore, CO_2 retention is probably occurring if PCO_2 approaches 40 mm Hg.

Elderly patients:

The elderly have a high prevalence of other obstructive lung disease (eg, COPD), so it is important to determine the magnitude of the reversible component of airflow obstruction (eg, by a 2- to 3-wk trial of inhaled corticosteroids or pulmonary function testing with bronchodilator challenge). The elderly may be more sensitive to adverse effects of β_2-agonists and inhaled corticosteroids. Patients requiring inhaled corticosteroids, particularly those with risk factors for osteoporosis, may benefit from measures to preserve bone density (eg, Ca and vitamin D supplements, bisphosphonates).

Equipment: class room, Harvey cardiopulmonary patient simulator, 6-channel ECG machine CARDIOLINE 100 L and Cardioline 200 + II S

Lesson time: 2 hours

Plan

I. Organization moments (Greeting, roll-call, theme announce, aim of lesson, applicants motivation to study the topic).

II. Control of basic knowledges (The task source for self-knowledge skills tests from «KROK2» - additional materials, cheking workbooks)

II.1 Requirements for theoretical readiness of applicants to perform practical classes.

Requirements to knowledges:

- Definition of bronchial asthma
- Modern aspects of etiology and pathophysiology of bronchial asthma
- Classification of bronchial asthma
- Clinical manifestation of bronchial asthma
- Laboratory and instrumental investigation of bronchial asthma
- Carry out differential diagnosis of bronchial asthma
- Complications of bronchial asthma
- Treatment, rehabilitation of patients with bronchial asthma
- Prognosis and disability of patients with bronchial asthma

List of didactic units

- To get a detailed anamnesis
- To do physical examination of patient, to diagnose and to estimate changes in condition
- To make a plan of additional investigation and estimate it

- Justify and make a preliminary and clinical diagnoses of bronchial asthma based on severity of airflow limitation, complex evaluation of bronchial asthma and make a group of patients.
- Basic principles of treatment stable bronchial asthma
- Estimation of exacerbation of bronchial asthma and its treatment
- Estimation of clinical examination, CBC, blood tests, sputum tests, spirometry, chest X-Ray and etc.

II.2 Questions (MSQ, clinical cases) for basic knowledge examination of topic

1. A man 62 y.old, who smokes for 40 years, complains of a nonproductive persistent cough during the last 12 years and has had a myocardial infarction, appeared dyspnea, edemas on ankles, and heaviness in the right hypochondriac. Dyspnea increases in a horizontal position and it can come to suffocation attacks. Suffocating cough obtained a constant character. Objectively: dry whistling rales in lungs. How can be this symptomatology explained?
   A. Progressing of a chronic obstructive pulmonary disease. +
   B. Joining of asthma to a chronic obstructive pulmonary disease.
   C. Cardio sclerosis and a development of a subacute left-ventricular weakness on its background.
   D. Possible malignant new growths of organs of a mediastinum.
   E. All the listed states.

2. A patient 28 y.old, has stuffiness in nose, attacks of expiratory suffocation at night time 1-2 times a week. A patient fell ill after acute respiratory viral infection, which he treated by himself with acetylsalicylic acid. Eosinophilia in blood and sputum analysis. The following can be suspected:
   A. Allergic bronchial asthma.
   B. Bronchial asthma of a physical effort.
   C. Aspirin asthma. +
   D. Exogenous allergic alveolitis.
   E. Eosinophylic infiltration of lungs.

3. A 54 y.o. male patient suffers from dyspnea during mild physical exertion, cough with sputum which is excreted with difficulty. On examination: diffuse cyanosis. Is Barrel-chest. Weakened vesicular breathing with prolonged expiration and dry whistling rales. AP is 140/80 mm Hg, pulse is 92 bpm, rhythmic. Spirography: vital capacity (VC)/predicted vital capacity- 65%, FEV1/FVC– 50%. Determine the type of respiratory insufficiency (RI).
   A. RI of restrictive type .
   B. RI of obstructive type . +
   C. RI of mixed type with prevailing obstruction.
   D. RI of mixed type with prevailing restriction.
   E. There is no RI.

4. A 18 y.old girl, whose mother suffers from allergic dermatitis, notices appearance of expiratory suffocation after taking sunflower seeds and sunflower oil. In the August a patient began to have sneezing, rhinitis, frequent suffocation attacks, which stopped in the end of September. What examinations are necessary for the revelation of the etiology of suffocation attacks?
   B. Scratch tests with tree pollen. +
   C. Scratch tests with meadow herbs pollen.
   D. Scratch tests with pollen of weed.
   E. Detection of a general IgE in blood.

E. Detection of a specific IgE for food allergens

5. A 42-year-old woman suffers from bronchial asthma, has an acute attack of bronchial asthma. What medication from the listed below is contraindicated to render a first aid?
   A.Euphylinum
   B.Izardin
   C.Corazolum
   D.Morphinum hydrochloride +

E.Strophanthin hydrochloride

6. A 38 y.o. woman is seriously ill. She complains of frequent paroxysms of expiratory dyspnea. The last paroxysm lasted over 12 hours and failed to respond to theophylline. The skin is palish gray, moist, RR 26/min. On auscultation, breath sounds are absent over some areas. Your preliminary diagnosis?

A.Bronchial asthma, acute severe asthma +
B.Chronic obstructive bronchitis
C.Atopic bronchial asthma, respiratory failure of the III degree
D.Bronchiectasis, respiratory failure of the II-III degree
E.Ischemic heart disease, pulmonary edema

7. A 27-year-old patient with a history of bronchial asthma was stung by a bee. He had a sensation of chest compression, breath shortage, difficult expiration, sense of heat in the upper half of body, dizziness, apparent itch, convulsions. Objectively: noisy wheezing breath, AP - 90/60 mm Hg, Ps-110 bpm. Auscultation revealed weak rhythmic heart sounds, rough respiration above lungs, sibilant rales. What drug group should be administered in the first place?

A.Glucocorticoids +
B.Methylxanthines
C.Cardiac glycosides
D.Anticonvulsive
E.Analgetics

8. A 20 y.o. patient with bronchial asthma experiences dyspnea attacks 3-4 times a week. Nocturnal attacks are 1 time a week. FEV1- 60% of predicted value, during the day it's variations is 32%. What is the severity of bronchial asthma condition?

A.Moderate severity condition +
B.Mild condition
C.Serious condition
D.Asthmatic status
E.Intermittent flow

9. A 37-year-old woman is sick with bronchial asthma for 15 years. Recently asthmatic attacks occur 4-5 times per week, night attacks -2-3 times per month. To stop attacks, the patient takes salbutamol. On physical exam: condition is relatively satisfactory. RR - 20/min, Ps is 76 bpm, BP - 120/80 mm Hg. Respiration in lungs is vesicular. Cardiac sounds are muted, rhythm is normal. What medication should be prescribed to prevent attacks of bronchial asthma on the first stage?

A. Inhalation of ant cholinergic long action
B.Inhalation of ant cholinergic short action
C.Inhalation of corticosteroids +
D.Per os corticosteroids
E.Injection of corticosteroids

10. A 49-year-old patient complains of dyspnea, cough. There are no sputum discharges. He has repeatedly used salbutamol but with no effect. Objectively: he is only able to sit while leaning on the table. Cyanosis of face, acrocyanosis are present. Breathing is shallow, labored, in some parts it cannot be auscultated; there are diffuse rales, expiration is significantly prolonged. Heart sounds are muffled, tachycardia is present. Ps - 112/min., AP- 110/70 mm Hg. Liver is located near the costal arch. There are no peripheral edema. What is your preliminary diagnosis?

A.Acute severe asthma +
B.Chronic obstructive bronchitis
C.Bronchial asthma, moderate gravity
D.Foreign object aspiration
E.Cardiac asthma

III. Proffesional skills formation (skills of patient`s management, treatment)

Professional algorithms: work with a patient (according to patients-students conversation algorithm).

During examination students must use next algorithm:

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Collecting data on patient complains, medical history, life history
5. Interpretation of clinical, laboratory and instrumental studies
6. Explanation for patient of next acting (hospitalization, workup)
7. End of conversation

Physical examination of patient with internal diseases

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Explanation of investigations are needed, taking agreement
5. Telling about possible negative feelings during investigation
6. Preparing to examination (clean warm hands, accurate nails, warm phonendoscope, screen if needed)
7. Examination (demonstration of clinical skills)
8. Interpretation of clinical, laboratory and instrumental studies
9. End of conversation

Telling to patient with internal diseases investigation results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of investigation results
5. Conversation with patient (comparing new and previous examination results, check if explanation is clear)
6. End of conversation

Planning and prognosing treatment results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of treatment
5. Conversation with patient (explanation of features taking pills, duration of taking drugs, possible side effects)
6. Check if explanation is clear
7. End of conversation

Telling treatment prognosis

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of expected treatment results
5. Conversation with patient (explanation of importance of life-long treatment, taking medications according to list, check if explanation is clear)
6. End of conversation

Task 1

1. Collecting complains, anamnesis, examination of patients with bronchial asthma
2. Identify clinical and instrumental symptoms
3. Make a syndrome based on symptoms
4. Identify the leading clinical syndrome

5. Assign laboratory and instrumental examination (CBC, urine analysis, blood tests, sputum tests, spirometry, bronchodilatation test, chest X-Ray, ECG, EchoCG and others)
6. Carry out differential diagnosis with COPD, pneumonia
7. Make a clinical diagnosis
8. Determine a degree of disability

Task 2

Prescribing different variants of treatment according to guidelines

Task 3

Work in Internet, work with thematic literature in department library room.
Student must fill patient examination protocol (example is added).

Control materials for final part of the lesson:

The cases for self-control with standard answers.

1. A 49-year-old patient complains of dyspnea, cough. There are no sputum discharges. He has repeatedly used salbutamol but with no effect. Objectively: he is only able to sit while leaning on the table. Cyanosis of face, acrocyanosis are present. Breathing is shallow, laboured, in some parts it cannot be auscultated; there are diffuse rales, expiration is significantly prolonged. Heart sounds are muffled, tachycardia is present. Ps - 112/min, AP- 110/70 mm Hg. Liver is located near the costal arch. There are no peripheral oedema. What is
your provisional diagnosis?
A Acute severe asthma
B Chronic obstructive bronchitis
C Bronchial asthma, moderate gravity
D Foreign object aspiration
E Cardiac asthma
2. A patient has severe asthma attack lasts more than 1 hour, despite the use of inhalation β2-adrenergic agonists, intravenous use euphylline and anticholinergic agents. What medications should supplement emergency therapy?
Blockers
A. β2-adrenergic agonists intravenously
B. NSAIDs per os
C. Corticosteroids inhalation
D. Corticosteroids intravenously
E. Antihistamines per os
3. Woman 40 y.o. was admitted to the hospital in serious condition. The forced position, orthopnea. There have been severe shortness of breath, shallow breathing. Neck veins expanded, skin was pale gray, wet. Barrel chest, intercostal spaces enlarged. Ps – 140 bpm. BP - 90/60 mmHg, deaf heart sounds. Above the lungs -breathing is not listening. What is the most likely diagnosis?
A. Acute severe asthma
B. Asthma exacerbation
C. Cardiac asthma
D. Pulmonary edema
E. Tracheobronchial dysfunction
4. Female 62 years old suffering from bronchial asthma. She complains of the appearance of cardiac chest pain, irregular pulse. OBJECTIVE: t -36,6 °C, Ps- 78 bpm, extrasystolic arrhythmia, BP-160/95 mmHg, RR 18 / min. In the lungs: harsh breathing with prolonged exhalation, scattered dry rales. Which drugs are contraindicated in this situation?

A. Furosemide
B. Nitrosorbide
C. Propranolol
D. Propafenone
E. Amlodipin

5. A 20 y.o. patient with bronchial asthma experiences dyspnea attacks 3-4 times a week. Nocturnal attacks are 1 time a week. FEV1- 50% , during the day it's variations is 25%. What is the severity of bronchial asthma condition?
A Moderate severity condition
B Mild condition
C Serious condition
D Asthmatic status
E Intermittent flow

6. A 27-year-old patient with a history of bronchial asthma was stung by a bee. He had a sensation of chest compression, breath shortage, difficult expiration, sense of heat in the upper half of body, dizziness, apparent itch, convulsions. Objectively: noisy wheezing breath, AP - 90/60 mm Hg, Ps-110 bpm. Auscultation revealed weak rhythmic heart sounds, harsh breathing above lungs, sibilant rales. What drug group should be administered in the first place?
A Analgetics
B Methylxanthines
C Cardiac glycosides
D Anticonvulsive
E Glucocorticoids

7. A 60 y.o. asthmatic man comes for a check up and complains that he is having some difficulty in "starting to urinate". Physical examination indicates that the man has blood pressure of 160/100 mm Hg, and a slight enlarged prostate. Which of the following medications would be useful in treating both of these conditions:
A Phetolamine
B Labetalol
C Doxazosin
D Propranolol
E Isoproterenol

8. A 18 y.old girl, whose mother suffers from allergic dermatitis, notices appearance of expiratory suffocation after taking sunflower seeds and sunflower oil. In the August a patient began to have sneezing, rhinitis, frequent suffocation attacks, which stopped in the end of September. What examinations are necessary for the revelation of the etiology of suffocation attacks?
A Scratch tests with tree pollen.
B Scratch tests with meadow herbs pollen.
C Scratch tests with pollen of weed.
D Detection of a general IgE in blood.
E. Detection of a specific IgE for food allergens

9. A 45-year-old man was brought to clinic with complaints of the pain that started suddenly in the left chest part and epigastric area, shortness of breath, nausea, one-time vomiting. The acute pain started after weight-lifting. On physical exam: shallow breathing, RR - 38/min, left chest part is behind during respiration, by percussion - tympanitic sound, respiration is not ausculated. Ps - 110 bpm, of weak filling. BP - 100/60 mm Hg, insignificant displacement of heart to the right, sounds are dull. What examination is the most expedient to do first?
A Bronchoscopy
B Electrocardiography
C Chest X-ray
D Esophagogastroscopy
E Ultrasound of the abdominal cavity

10. Pregnant 25 y.o. with a history of allergy (pollinosis), 28 weeks of pregnancy, after the stressful situation suddenly appeared noisy wheezing, dyspnea, face cyanosis. Auscultation: weakened breathing, dry whistling rales; percussion - box sound. After the attack the woman expectorated small amount of viscous sputum. What is the most likely diagnosis?
A Bronchial asthma attack.
B Pulmonary edema.
C Chronic obstructive pulmonary disease
D Pulmonary embolism.
E Threatened miscarriage.

Standard answers: 1-A, 2-D, 3-A, 4-C, 5-A, 6-E, 7-C, 8-B, 9-C, 10-A.

IV. Making conclusions, telling final marks, tasks for the next lesson

Literature list:
- Basic literature source:
1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention (2020 Update).
http://www.ginasthma.org/
2. 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

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European female of 35 years old.
Complaints: For daily attacks of suffocation, up to 6 times a day, including nighttime.
They arise during intense physical exertion, inhalation of frosty air on house dust (with sneezing), on the smell of prfumes. Accompanied by wheezing, wheezing in the chest and cough (dry). Shortness of breath of a mixed nature, which occurs with physical exertion, when climbing 3 flight of stairs, disappears after rest.The cough is periodic, with gray sputum, in moderate amount, viscous, odorless.
Medical history: Considers herself ill for about 2 months, when coughing appeared after starting work at bakery
Life history: Material and living conditions are satisfactory. Tuberculosis, venereal disease,
denies. No any allergic reaction to the medications. Works in bakery with flour. Hereditary history is not burdened. Does not smoke, does not abuse alcohol. Gynecological history: there were no pregnancies, no births. She has not been in contact with infectious patients in the last 3 days. She has not left the country for the last 3 years.
Objective status: The general condition of the patient is of moderate severity,
clear consciousness. The physique is correct. The position in bed is active.
The skin and visible mucous membranes are clear, pale. Subcutaneous fat is
developed evenly, with some excess in the abdomen. Nutrition normal. Body mass index = 23 kg/m2. Breathing over the lungs is vesicular, diffuse wheezing sounds. Percussion - clear pulmonary sound. Breath rate - 17 / min. BP –120/80 mm Hg symmetrical on both hands. Heart rhythm is regular, heart rate – 80 beats. in 1 min. Heart sounds are clear. The abdomen is soft and painless on palpation. The liver and spleen are not palpable. The symptom of tapping on the lumbar region is negative. No peripheral edema.
Examination plan:

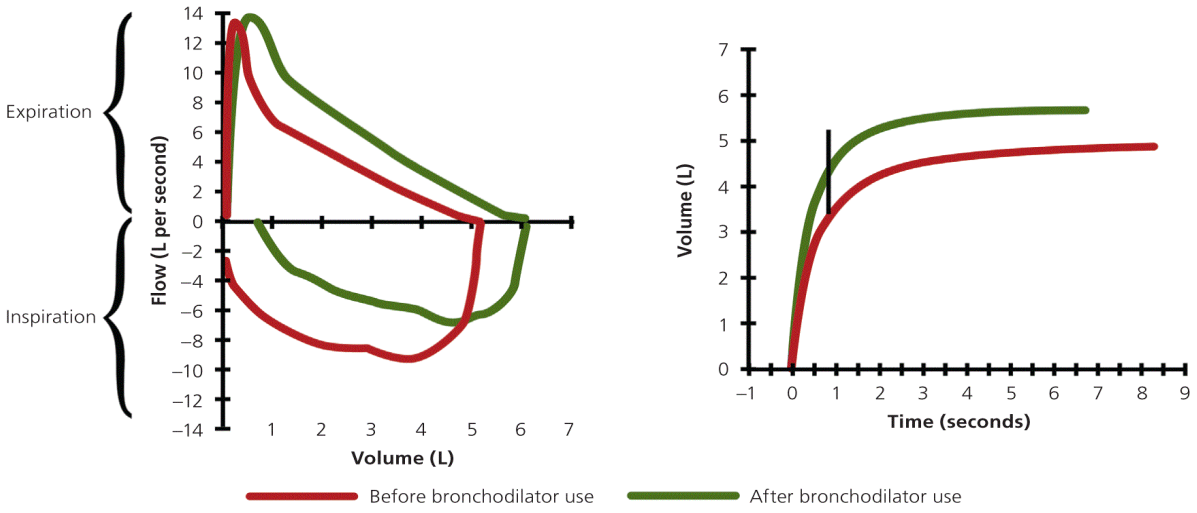
1. Cell blood count,
2. blood biochemistry: creatinine, urea, albumin
3. coagulation test,
4. liver function tests
5. allergy tests
6. Ig E
6. Spirometry
7. ECG
8. Chest X-ray
9. Sputum test

Patient has positive allergy test on flour. Another analysis are normal

Spirometry

Age: 35 years

	Prebronchodilators				*Postbronchodilators*		
Spirometry	*Predicted*	*LLN*	*Actual*	*% of predicted*	*Actual*	*% of predicted*	*% change*
FVC (L)	5.20	4.34	5.18[A]	99[D]	6.06[F]	116	+16[I]
FEV_1 (L)	4.37	3.64	3.55[B]	81[E]	4.64[G]	106	+30[J]
FEV_1/FVC (%)	84	75	68[C]	81	77[H]	91	+11
$FEF_{25\%-75\%}$ (L per second)	4.74	3.11	2.41	50	3.84	80	+59



A = FVC (before bronchodilators), this is > LLN and thus does not show a restrictive pattern
B = FEV_1 (before bronchodilators)
C = FEV_1/FVC ratio (before bronchodilators), this is < LLN and thus shows an obstructive defect
D = FVC percentage of predicted (before bronchodilators)
E = FEV_1 percentage of predicted (before bronchodilators)
F = FVC (after bronchodilators)
G = FEV_1 (after bronchodilators)
H = FEV_1/FVC ratio (after bronchodilators)
I = A 0.88-L increase in FVC is a 16% increase
J = A 1.09-L increase in FEV_1 is a 30% increase

The above indicates reversibility because at least one of the two (FVC or FEV_1) increased by at least 0.2 L and by at least 12%

Diagnosis:
Professional bronchial asthma, uncontrolled, mild form
Treatment plan:

1. Refusing from working with allergen (flour)
2. Salmeterol 50 mcg in inhaler, 3 months
3. Flutikazon 100 mcg in inhaler, 3 months
4. Ambroxol 15 mg 2 times per day, 5 days

After 3 months doctor must see result of control spirometry and decide for prolongation of using inhalers.

Practical lesson № 14

Theme: Pneumonias

Object: To teach applicants to master the method of examination of patients with respiratory diseases with the selection of the main pulmonological syndromes. To study probable etiological factors, pathogenesis of chronic obstructive pulmonary diseases, their main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis and efficiency of patients.

Basic concepts

№	Term	Definition
1	Community-acquired pneumonia	develops in people with limited or no contact with medical institutions or settings
2	Hospital-acquired pneumonia	develops at least 48 h after hospital admission
3	Nursing home–acquired pneumonia	Develops in patients who lives in nursing home
4	Aspiration pneumonia	are caused by inhaling toxic substances, usually gastric contents, into the lungs
5	Pneumonia in immunocompromised patients	is often caused by unusual pathogen

Pneumonia is sometimes referred to as the forgotten killer. The World Health Organization estimates that lower respiratory tract infection is the most common infectious cause of death in the world (the third most common cause overall), with almost 3.5 million deaths yearly. Together, pneumonia and influenza constitute the ninth leading cause of death in the United States, resulting in 50,000 estimated deaths in 2018. This number is probably underestimated, since deaths from sepsis (for which pneumonia is the most common source) and deaths attributed to other conditions (e.g., cancer and Alzheimer's disease) for which pneumonia is the terminal event are coded separately.

Pneumonia is acute inflammation of the lungs caused by infection. Initial diagnosis is usually based on chest x-ray and clinical findings. Causes, symptoms, treatment, preventive measures, and prognosis differ depending on whether the infection is bacterial, viral, fungal, or parasitic; whether it is acquired in the community, hospital, or other health care–associated location; and whether it develops in a patient who is immunocompetent or immunocompromised.

The **most common cause** of pneumonia in adults > 30 yr is

- Bacteria

Streptococcus pneumoniae infection is the most common pathogen in all age groups, settings, and geographic regions. However, pathogens of every sort, from viruses to parasites, can cause pneumonia.

The airways and lungs are constantly exposed to pathogens in the external environment; the upper airways and oropharynx in particular are colonized with so-called normal flora. Microaspiration of these pathogens from the upper respiratory tract is a regular occurrence, but these pathogens are readily dealt with by lung host defense mechanisms. Pneumonia develops when

- Defense mechanisms are compromised
- Macroaspiration leads to a large inoculum of bacteria that overwhelms normal host defenses
- A particularly virulent pathogen is introduced

Occasionally, infection develops when pathogens reach the lungs via the bloodstream or by contiguous spread from the chest wall or mediastinum.

Upper airway defenses include salivary IgA, proteases, and lysozymes; growth inhibitors produced by normal flora; and fibronectin, which coats the mucosa and inhibits adherence.
Nonspecific **lower airway defenses** include cough, mucociliary clearance, and airway angulation preventing infection in airspaces. Specific lower airway defenses include various pathogen-specific immune mechanisms, including IgA and IgG opsonization, antimicrobial peptides, anti-inflammatory effects of surfactant, phagocytosis by alveolar macrophages, and T-cell–mediated immune responses. These mechanisms protect most people against infection.
Numerous conditions alter the normal flora (eg, systemic illness, undernutrition, hospital or nursing home exposure, antibiotic exposure) or impair these defenses (eg, altered mental status, cigarette smoking, nasogastric or endotracheal intubation). Pathogens that then reach airspaces can multiply and cause pneumonia.

Specific pathogens causing pneumonia cannot be found in < 50% of patients, even with extensive diagnostic investigation, primarily because of the limitations of currently available diagnostic tests. But because pathogens and outcomes tend to be similar in patients in similar settings and with similar risk factors, pneumonias can be categorized as

- Community-acquired
- Hospital-acquired (including ventilator-acquired and postoperative pneumonia
- Health care–associated (including nursing home-acquired pneumonia)
- Occurring in immunocompromised patients, including patients with HIV infection
- Aspiration pneumonia, which occur when large volumes of upper airway or gastric secretions enter into the lungs

These categorizations allow treatment to be selected empirically.
The term interstitial pneumonia refers to various unrelated conditions of varied and sometimes unknown causes characterized by inflammation and fibrosis of the pulmonary interstitium.

Specific pathogens causing pneumonia cannot be found in < 50% of patients, even with extensive diagnostic investigation. But because pathogens and outcomes tend to be similar by setting and host risk factors, pneumonias can be categorized as

- Community-acquired
- Hospital-acquired (including ventilator-acquired and postoperative)
- Nursing home–acquired
- Occurring in immunocompromised people

These categorizations allow treatment to be selected empirically.

Community-acquired pneumonia

develops in people with limited or no contact with medical institutions or settings. The most commonly identified pathogens are Streptococcus pneumoniae, Haemophilus influenzae, and atypical organisms (ie, Chlamydia pneumoniae, Mycoplasma pneumoniae, Legionellasp). Symptoms and signs are fever, cough, pleuritic chest pain, dyspnea, tachypnea, and tachycardia. Diagnosis is based on clinical presentation and chest x-ray. Treatment is with empirically chosen antibiotics. Prognosis is excellent for relatively young or healthy patients, but many pneumonias, especially when caused by S. pneumoniae or influenza virus, are fatal in older, sicker patients.

Etiology

Many organisms cause community-acquired pneumonia, including bacteria, viruses, and fungi. Pathogens vary by patient age and other factors, but the relative importance of each as a cause of community-acquired pneumonia is uncertain, because most patients do not undergo thorough testing, and because even with testing, specific agents are identified in < 50% of cases.
S. pneumoniae, *H. influenzae*, *C. pneumoniae*, and *M. pneumoniae*are the most common bacterial causes. Pneumonias caused by chlamydia and mycoplasma are often clinically indistinguishable from other pneumonias. Common viral agents include respiratory syncytial virus (RSV), adenovirus, influenza viruses, metapneumovirus, and parainfluenza viruses. Bacterial superinfection can make distinguishing viral from bacterial infection difficult.

C. pneumoniae accounts for 2 to 5% of community-acquired pneumonia and is the 2nd most common cause of lung infections in healthy people aged 5 to 35 yr. *C. pneumoniae* is commonly responsible for outbreaks of respiratory infection within families, in college dormitories, and in military training camps. It causes a relatively benign form of pneumonia that infrequently requires hospitalization. *Chlamydia psittaci*pneumonia (psittacosis) is rare and occurs in patients who own or are often exposed to birds.

Since the year 2000, the incidence of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA) skin infections has increased markedly. This pathogen can rarely cause severe, cavitating pneumonia and tends to affect young adults.

P. aeruginosa is an especially common cause of pneumonia in patients with cystic fibrosis, neutropenia, advanced AIDS, and/or bronchiectasis.

A host of other organisms causes lung infection in immunocompetent patients. In patients with pneumonia, a thorough history of exposures, travel, pets, hobbies, and other exposures is essential to raise suspicion of less common organisms.

Q fever, tularemia, anthrax, and plague are uncommon bacterial syndromes in which pneumonia may be a prominent feature. Tularemia , anthrax and plague should raise the suspicion of bioterrorism.

Adenovirus, Epstein-Barr virus, and coxsackievirus are common viruses that rarely cause pneumonia. Seasonal influenza can rarely cause a direct viral pneumonia but often predisposes to the development of a serious secondary bacterial pneumonia. Varicella virus and hantavirus cause lung infection as part of adult chickenpox and hantavirus pulmonary syndrome. A coronavirus causes severe acute respiratory syndrome (SARS) and the Middle East Respiratory syndrome (MERS).

Common fungal pathogens include *Histoplasma capsulatum* (histoplasmosis) and *Coccidioides immitis* (coccidioidomycosis). Less common fungal pathogens include *Blastomyces dermatitidis* (blastomycosis) and *Paracoccidioides braziliensis* (paracoccidioidomycosis). *Pneumocystis jirovecii* commonly causes pneumonia in patients who have HIV infection or are immunosuppressed.

Parasites causing lung infection in developed countries include *Toxocara canis* or *T. catis* (visceral larva migrans—Toxocariasis), *Dirofilaria immitis* (dirofilariasis), and *Paragonimus westermani* (paragonimiasis).

Symptoms and Signs

Symptoms include malaise, cough, dyspnea, and chest pain. Cough typically is productive in older children and adults and dry in infants, young children, and the elderly. Dyspnea usually is mild and exertional and is rarely present at rest. Chest pain is pleuritic and is adjacent to the infected area. Pneumonia may manifest as upper abdominal pain when lower lobe infection irritates the diaphragm. Symptoms become variable at the extremes of age. Infection in infants may manifest as nonspecific irritability and restlessness; in the elderly, as confusion and obtundation.

Signs include fever, tachypnea, tachycardia, crackles, bronchial breath sounds, egophony, and dullness to percussion. Signs of pleural effusion may also be present.

Nasal flaring, use of accessory muscles, and cyanosis are common among infants. Fever is frequently absent in the elderly.

Symptoms and signs were previously thought to differ by type of pathogen, but presentations overlap considerably. In addition, no single symptom or sign is sensitive or specific enough to predict the organism. Symptoms are even similar for noninfective lung diseases such as pulmonary embolism, pulmonary cancer, and other inflammatory lung diseases.

Diagnosis

- Chest x-ray
- Consideration of alternative diagnoses (eg, heart failure, pulmonary embolism)
- Sometimes identification of pathogen

Diagnosis is suspected on the basis of clinical presentation and infiltrate seen on chest x-ray. When there is high clinical suspicion of pneumonia and the chest x-ray does not reveal an infiltrate, doing CT or repeating the chest x-ray in 24 to 48 h is recommended.

Differential diagnosis in patients presenting with pneumonia-like symptoms includes heart failure and COPD exacerbation. Other disorders should be considered, particularly when findings are inconsistent or not typical. The most serious common misdiagnosis is pulmonary embolism, which may be more likely in patients with minimal sputum production, no accompanying URI or systemic symptoms, and risk factors for thromboembolism; thus, testing for pulmonary embolism should be considered. Quantitative cultures of bronchoscopic or suctioned specimens, if they are obtained before antibiotic administration, can help distinguish between bacterial colonization (ie, presence of microorganisms at levels that provoke neither symptoms nor an immune response) and infection. However, bronchoscopy is usually done only in patients receiving mechanical ventilation or for those with other risk factors for unusual microorganisms or complicated pneumonia (eg, immunocompromise, failure of empiric therapy).

Distinguishing between bacterial and viral pneumonias is challenging. Many studies have investigated the utility of clinical, imaging, and routine blood tests, but no test is reliable enough to make this differentiation. The use of serum biomarkers, such as procalcitonin and C-reactive protein (CRP), to help in differentiating bacterial from nonbacterial pneumonia is currently under investigation.

In outpatients with mild or moderate pneumonia, no further diagnostic testing is needed (see Table: Risk Stratification for Community-Acquired Pneumonia (the Pneumonia Severity Index)). In patients with moderate or severe pneumonia, a WBC count and electrolytes, BUN, and creatinine are useful to classify risk and hydration status. Pulse oximetry or ABG testing should also be done to assess oxygenation. For patients with moderate or severe pneumonia who require hospitalization, 2 sets of blood cultures are obtained to assess for bacteremia and sepsis. The IDSA provides a guide to recommended testing based on patient demographic and risk factors
(Infectious Diseases Society of America Clinical Guideline on Community-Acquired Pneumonia).

Pathogens:

Identification of the pathogen can be useful to direct therapy and verify bacterial susceptibilities to antibiotics. However, because of the limitations of current diagnostic tests and the success of empiric antibiotic treatment, experts recommend limiting attempts at microbiologic identification (eg, cultures, specific antigen testing) unless patients are at high risk or have complications (eg, severe pneumonia, immunocompromise, asplenia, failure to respond to empiric therapy). In general, the milder the pneumonia, the less such diagnostic testing is required. Critically ill patients require the most intensive testing, as do patients in whom a antibiotic-resistant or unusual organism is suspected (eg, TB, *P. jirovecii*) and patients whose condition is deteriorating or who are not responding to treatment within 72 h.

Chest x-ray findings generally cannot distinguish one type of infection from another, although the following findings are suggestive:

- Multilobar infiltrates suggest *S. pneumoniae* or *Legionella pneumophila* infection.
- Interstitial pneumonia (on chest x-ray, appearing as increased interstial markings, subpleural reticular opacities that increase from the apex to the bases of the lungs, and peripheral honeycombing) suggests viral or mycoplasmal etiology.
- Cavitating pneumonia suggests *S. aureus* or a fungal or mycoplasmal etiology.

Blood cultures, which are often obtained in patients hospitalized for pneumonia, can identify causative bacterial pathogens if bacteremia is present. About 12% of all patients hospitalized with pneumonia have bacteremia; *S. pneumoniae* accounts for two thirds of these cases.

Sputum testing can include Gram stain and culture for identification of the pathogen, but the value of these tests is uncertain because specimens often are contaminated with oral flora and overall diagnostic yield is low. Regardless, identification of a bacterial pathogen in sputum cultures allows for susceptibility testing. Obtaining sputum samples also allows for testing for viral pathogens via direct fluorescence antibody testing or PCR, but caution needs to be exercised in interpretation

because 15% of healthy adults carry a respiratory virus or potential bacterial pathogen. In patients whose condition is deteriorating and in those unresponsive to broad-spectrum antibiotics, sputum should be tested with mycobacterial and fungal stains and cultures.

Sputum samples can be obtained noninvasively by simple expectoration or after hypertonic saline nebulization (induced sputum) for patients unable to produce sputum. Alternatively, patients can undergo bronchoscopy or endotracheal suctioning, either of which can be easily done through an endotracheal tube in mechanically ventilated patients. Otherwise, bronchoscopic sampling is usually done only for patients with other risk factors (eg, immunocompromise, failure of empiric therapy).

Urine testing for *Legionella* antigen and pneumococcal antigen is now widely available. These tests are simple and rapid and have higher sensitivity and specificity than sputum Gram stain and culture for these pathogens. Patients at risk of *Legionella* pneumonia (eg, severe illness, failure of outpatient antibiotic treatment, presence of pleural effusion, active alcohol abuse, recent travel) should undergo testing for urinary *Legionella* antigen, which remains present long after treatment is initiated, but the test detects only *L. pneumophila* serogroup 1 (70% of cases).

The **pneumococcal antigen test** is recommended for patients who are severely ill; have had unsuccessful outpatient antibiotic treatment; or who have pleural effusion, active alcohol abuse, severe liver disease, or asplenia. This test is especially useful if adequate sputum samples or blood cultures were not obtained before initiation of antibiotic therapy. A positive test can be used to tailor antibiotic therapy, though it does not provide antimicrobial susceptibility

Treatment

- Risk stratification for determination of site of care
- Antibiotics
- Antivirals for influenza or varicella
- Supportive measures

Risk stratification

Risk stratification via risk prediction rules may be used to estimate mortality risk and can help guide decisions regarding hospitalization. These rules have been used to identify patients who can be safely treated as outpatients and those who require hospitalization because of high risk of complications (Risk Stratification for Community-Acquired Pneumonia (the Pneumonia Severity Index)). However, these rules should supplement, not replace, clinical judgment because many unrepresented factors, such as likelihood of adherence, ability to care for self, and wish to avoid hospitalization, should also influence triage decisions. An. ICU admission is required for patients who

- Need mechanical ventilation
- Have hypotension (systolic BP ≤ 90 mm Hg) that is unresponsive to volume resuscitation

Other criteria that mandate consideration of ICU admission include

- Respiratory rate >30/min
- Pa o_2/fraction of inspired O_2 ($F io_2$) < 250
- Multilobar pneumonia
- Diastolic BP < 60 mm Hg
- Confusion
- BUN > 19.6 mg/dL

The Pneumonia Severity Index (PSI) is the most studied and validated prediction rule. However, because the PSI is complex and requires several laboratory assessments, simpler rules such as CURB-65 are usually recommended for clinical use. Use of these prediction rules has led to a reduction in unnecessary hospitalizations for patients who have milder illness.

In CURB-65, 1 point is allotted for each of the following risk factors:

- **C** onfusion
- **U** remia (BUN ≥19 mg/dL)
- **R** espiratory rate > 30 breaths/min
- Systolic **BP** < 90 mm Hg or diastolic BP ≤ 60 mm Hg

- Age ≥ **65** yr

Scores can be used as follows:

- 0 or 1 points: Risk of death is < 3%. Outpatient therapy is usually appropriate.
- 2 points: Risk of death is 9%. Hospitalization should be considered.
- ≥ 3 points: Risk of death is 15 to 40%. Hospitalization is indicated, and, particularly with 4 or 5 points, ICU admission should be considered.

Antimicrobials

Antibiotic therapy is the mainstay of treatment for community-acquired pneumonia. Appropriate treatment involves starting empiric antibiotics as soon as possible, preferably ≤8 h after presentation. Because organisms are difficult to identify, the empiric antibiotic regimen is selected based on likely pathogens and severity of illness. Consensus guidelines have been developed by many professional organizations; one widely used set is detailed in Community-Acquired Pneumonia in Adults (see also Infectious Diseases Society of America Clinical Guideline on Community-Acquired Pneumonia). Guidelines should be adapted to local susceptibility patterns, drug formularies, and individual patient circumstances. If a pathogen is subsequently identified, the results of antibiotic susceptibility testing can help guide any changes in antibiotic therapy.

With empiric treatment, 90% of patients with bacterial pneumonia improve. Improvement is manifested by decreased cough and dyspnea, defervescence, relief of chest pain, and decline in WBC count. Failure to improve should trigger suspicion of

- An unusual organism
- Resistance to the antimicrobial used for treatment
- Empyema
- Coinfection or superinfection with a 2nd infectious agent
- An obstructive endobronchial lesion
- Immunosuppression
- Metastatic focus of infection with reseeding (in the case of pneumococcal infection)
- Nonadherence to treatment (in the case of outpatients)

If none of these conditions can be proved, treatment failure is likely due to inadequate host defenses. When therapy has failed, consultation with a pulmonary and/or infectious disease specialist is indicated.

Antiviral therapy may be indicated for select viral pneumonias. Ribavirin is not used routinely for RSV pneumonia in children or adults, but may be used in occasional high-risk children age < 24 mo.

Oseltamivir 75 mg po bid or zanamivir 10 mg inhaled bid started within 48 h of symptom onset and given for 5 days reduces the duration and severity of symptoms in patients who develop influenza infection. In patients hospitalized with confirmed influenza infection, observational studies suggest benefit even 48 h after symptom onset.

Acyclovir 5 to 10 mg/kg IV q 8 h for adults or 250 to 500 mg/m ^{2} body surface area IV q 8 h for children is recommended for varicella lung infections. Though pure viral pneumonia does occur, superimposed bacterial infections are common and require antibiotics directed against *S. pneumoniae*, *H. influenzae*, and *S. aureus*.

Follow-up x-rays should be obtained 6 wk after treatment in patients > 35; persistence of an infiltrate at ≥ 6 wk raises suspicions of TB or an underlying, possibly malignant endobronchial lesion.

Community-Acquired Pneumonia in Adults

Group	Likely Organisms	Empiric Treatment
I. Outpatients—no modifying factors present †	*Streptococcus pneumoniae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Haemophilus influenzae*, respiratory viruses,	Macrolide (azithromycin 500 mg po once, then 250 mg once/day; clarithromycin 250 to 500 mg po bid; or extended-release clarithromycin 1 g

	miscellaneous organisms (eg, *Legionella* sp, *Mycobacterium tuberculosis*, endemic fungi)	once/day) *or* Doxycycline 100 mg po bid (if allergic to macrolide)
II. Outpatients—modifying factors present †	*S. pneumoniae*, including antibiotic-resistant forms; *M. pneumoniae*; *C. pneumoniae*; mixed infection (bacteria + atypical pathogen or virus); *H. influenzae*; enteric gram-negative organisms; respiratory viruses; miscellaneous organisms (eg, *Moraxella catarrhalis*, *Legionella* sp, anaerobes [aspiration], *M. tuberculosis*, endemic fungi)	β-Lactam (cefpodoxime 200 mg po q 12 h; cefuroxime 500 mg po q 12 h; amoxicillin 1 g q 8 h; amoxicillin/clavulanate 875/125 mg q 12 h) *plus* Macrolide po *or* Antipneumococcal fluoroquinolone po or IV (alone; eg, moxifloxacin [400 mg po/IV q 24 h], gemifloxacin [320 mg po/IV q 24 h], levofloxacin [750 mg po/IV q 24 h])
III. Inpatient—not in ICU	*S. pneumoniae*, *H. influenzae*; *M. pneumoniae*; *C. pneumoniae*; mixed infection (bacteria + atypical pathogen or virus); respiratory viruses; *Legionella* sp, miscellaneous organisms (eg, *M. tuberculosis*, endemic fungi, *Pneumocystis jirovecii*)	Azithromycin 500 mg IV q 24 h *plus* β-Lactam IV (cefotaxime 1 to 2 g q 8 to 12 h; ceftriaxone 1 g q 24 h) *or* Antipneumococcal fluoroquinolone po or IV (alone)
IVA. ICU patient—no *Pseudomonas* risk factors	*S. pneumoniae*, including antibiotic-resistant forms; *Legionella* sp; *H. influenzae*; enteric gram-negative organisms,; *Staphylococcus aureus*; *M. pneumoniae*; respiratory viruses miscellaneous organisms (eg, *C. pneumoniae*, *M. tuberculosis*, endemic fungi)	β-Lactam IV (cefotaxime 1 to 2 g IV q 8 to 12 h; ceftriaxone 1 g IV q 24 h) *plus either* Antipneumococcal fluoroquinolone IV *or* Azithromycin 500 mg IV q 24 h
IVB. ICU patient—*Pseudomonas* risk factors present	Same as those for category IVA (above) plus *Pseudomonas* sp	Antipseudomonal β-lactam ‡ or aztreonam (if allergic to or intolerant of β-lactams) 1 to 2 g q 8 h *plus either* Ciprofloxacin 400 mg IV q 12 h or levofloxacin 750 mg po or IV q 24 h Alternatively: Antipseudomonal β-lactam ‡ *plus* An aminoglycoside *plus either* Ciprofloxacin 400 mg IV q 12 h or levofloxacin 750 mg po

		or IV q 24 h

*These guidelines do not apply to patients with immunosuppression, influenza, aspiration pneumonia, or health care–associated pneumonia.

† Modifying factors:

- *Increased risk of antibiotic-resistant organisms:* Age > 65, alcoholism, antibiotic within 3 mo, exposure to child in day care center, multiple coexisting illnesses.
- *Increased risk of enteric gram-negative organisms:* Antibiotic use within 3 mo, cardiopulmonary disease (including COPD and heart failure), multiple coexisting illnesses.
- *Increased risk of Pseudomonas aeruginosa*: Broad-spectrum antibiotics > 7 days in past month, corticosteroid use, undernutrition, structural pulmonary disease.

‡ Antipseudomonal β-lactams =cefepime 1 to 2 g IV q 12 h, imipenem 500 mg IV q 6 h, meropenem 500 mg to 1 g IV q 8 h, piperacillin/tazobactam 3.375 g IV q 4 h.

Supportive care

Supportive care includes fluids, antipyretics, analgesics, and, for patients with hypoxemia, O_2. Prophylaxis against thromboembolic disease and early mobilization improve outcomes for patients hospitalized with pneumonia. Cessation counseling should also be done for smokers.

Hospital-acquired pneumonia (HAP)

Hospital-acquired pneumonia (HAP) develops at least 48 h after hospital admission. The most common pathogens are gram-negative bacilli and Staphylococcus aureus; drug-resistant organisms are an important concern. Symptoms and signs are the same as those for community-acquired pneumonia, but in ventilated patients, pneumonia may also manifest as worsening oxygenation and increased tracheal secretions. Diagnosis is suspected on the basis of clinical presentation and chest x-ray and is confirmed by blood culture or bronchoscopic sampling of the lower respiratory tract. Treatment is with antibiotics. Overall prognosis is poor, due in part to comorbidities.

HAP includes ventilator-associated pneumonia (VAP), postoperative pneumonia, and pneumonia that develops in unventilated but otherwise moderately or critically ill hospitalized inpatients. It also includes the new category healthcare-associated pneumonia (HCAP), which refers to pneumonia acquired by patients in healthcare facilities such as chronic care facilities, dialysis centers, and infusion centers.

Etiology

The most common cause is microaspiration of bacteria that colonize the oropharynx and upper airways in seriously ill patients.

Risk factors:

Endotracheal intubation with mechanical ventilation poses the greatest overall risk; VAP constitutes > 85% of all cases, with pneumonia occurring in 17 to 23% of ventilated patients. Endotracheal intubation breaches airway defenses, impairs cough and mucociliary clearance, and facilitates microaspiration of bacteria-laden secretions that pool above the inflated endotracheal tube cuff. In addition, bacteria form a biofilm on and within the endotracheal tube that protects them from antibiotics and host defenses.

In nonintubated patients, risk factors include previous antibiotic treatment, high gastric pH (due to stress ulcer prophylaxis or therapy), and coexisting cardiac, pulmonary, hepatic, or renal insufficiency. Major risk factors for postoperative pneumonia are age > 70, abdominal or thoracic surgery, and dependent functional status.

Pathogens:

Pathogens and antibiotic resistance patterns vary significantly among institutions and can vary within institutions over short periods (eg, month to month). In general, the most important pathogen is Pseudomonas aeruginosa, which is especially common in pneumonias acquired in intensive care

settings and in patients with cystic fibrosis, neutropenia, advanced AIDS, and bronchiectasis. Other important pathogens include enteric gram-negative bacteria (mainly Enterobactersp, Klebsiella pneumoniae, Escherichia coli, Serratia marcescens, Proteus sp, and Acinetobacter sp) and both methicillin-sensitive and methicillin-resistant Staphylococcus aureus.

S. aureus, Streptococcus pneumoniae, and Haemophilus influenzae are most commonly implicated when pneumonia develops within 4 to 7 days of hospitalization, whereas enteric gram-negative organisms become more common with increasing duration of intubation. Patients with HAP due to S. aureus or gram-negative bacilli tend to be elderly or have serious circumstances, such as needing a ventilator, undergoing chemotherapy for cancer, or having chronic pulmonary disease.

Prior antibiotic treatment greatly increases the likelihood of polymicrobial infection, resistant organisms, particularly methicillin-resistant S. aureus, and Pseudomonas infection. Infection with a resistant organism markedly worsens mortality and morbidity.

High-dose corticosteroids increase the risk of Legionella and Pseudomonas infections.

Symptoms and Signs

Symptoms and signs in nonintubated patients are generally the same as those for community-acquired pneumonia. Pneumonia in critically ill, mechanically ventilated patients more typically causes fever and increased respiratory rate or heart rate or changes in respiratory parameters, such as an increase in purulent secretions or worsening hypoxemia.

Diagnosis

- Chest x-ray and clinical criteria (limited accuracy)
- Sometimes bronchoscopy, blood cultures

Diagnosis is imperfect. In practice, HAP is often suspected on the basis of the appearance of a new infiltrate on a chest x-ray that is taken for evaluation of new symptoms or signs or of leukocytosis. However, no symptom, sign, or x-ray finding is sensitive or specific for the diagnosis, because all can be caused by atelectasis, pulmonary embolism, or pulmonary edema and may be part of the clinical findings in acute respiratory distress syndrome. Alternative diagnoses should be sought, particularly in patients who have a pneumonia risk score < 6.

Gram stain and culture of endotracheal aspirates are of uncertain benefit, because specimens are likely to be contaminated with bacteria that are colonizers as well as pathogens, and a positive culture may or may not indicate infection. Bronchoscopic sampling of lower airway secretions for quantitative culture seems to yield more reliable specimens, but the effect of this approach on outcomes is undetermined. Measurement of inflammatory mediators in bronchoalveolar lavage fluid may play a future role in diagnosis; eg, a concentration of soluble triggering receptor expressed on myeloid cells (a protein expressed and shed by immune cells during infection) > 5 pg/mL may help distinguish bacterial and fungal pneumonia from noninfectious causes of clinical and radiographic changes in ventilated patients. However, this approach requires further investigation. The only finding that reliably identifies both pneumonia and the responsible organism is a pleural fluid culture that is positive for a respiratory pathogen. Blood cultures are relatively specific if a respiratory pathogen is identified but are insensitive.

Prognosis

The mortality associated with HAP due to gram-negative infection is about 25 to 50% despite the availability of effective antibiotics. Whether death is due to underlying illness or to the pneumonia itself is uncertain. Women may be at greater risk of death. The mortality rate with *S. aureus*pneumonia is 10 to 40%, in part due to the serious circumstances with which it is associated.

Treatment

Empirically chosen antibiotics active against resistant gram-negative and gram-positive organisms

If the diagnosis is suspected, treatment is with antibiotics that are chosen empirically based on local sensitivity patterns, specific patient risk factors, and the conditions noted previously. Indiscriminate use of antibiotics is a major contributor to development of antimicrobial resistance. Therefore, treatment may begin with initial use of broad-spectrum drugs, which are replaced by the most specific drug available for the pathogens identified by culture. Alternative strategies for limiting resistance that have not proved effective include stopping antibiotics after 72 h in patients whose

pulmonary infection scores improve to < 6 and regularly rotating empirically chosen antibiotics (eg, q 3 to 6 mo).

Multiple regimens exist, but all should include antibiotics that are effective against both resistant gram-negative and gram-positive organisms. Options include

- A carbapenem (imipenem/cilastatin 500 mg IV q 6 h or 1 g q 8 h or meropenem 1 g IV q 8 h), monobactam (aztreonam 1 to 2 g IV q 8 h), or piperacillin/tazobactam 4.5 g q 6 h
- Ceftazidime 2 g IV q 8 h or cefepime 1 to 2 g q 8 to 12 h
- These drugs are given alone or combined with vancomycin15 mg/kg q 12 h

Linezolid 600 mg IV q 12 h may be used for some pulmonary infections involving methicillin-resistant*S. aureus*. Daptomycin should not be used for pulmonary infections.

Prevention

Most measures focus on preventing VAP. Semiupright or upright positioning reduces risk of aspiration and pneumonia compared with recumbent positioning and is the simplest and most effective preventive method. Noninvasive ventilation using continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) prevents the breach in airway defense that occurs with endotracheal intubation and eliminates the need for intubation in some patients.

Continuous aspiration of subglottic secretions using a specially designed endotracheal tube attached to a suction device seems to reduce the risk of aspiration.

Selective decontamination of the oropharynx (using topical gentamicin, colistin, chlorhexidine, vancomycin cream, or a combination) or of the entire GI tract (using polymyxin, an aminoglycoside or quinolone, and either nystatin or amphotericin B) is controversial because of concerns about resistant strains and because decontamination, although it decreases incidence of HAP, has not been shown to decrease mortality.

Surveillance cultures and routinely changing ventilator circuits or endotracheal tubes have not been shown to decrease VAP.

Incentive spirometry is recommended to help prevent postoperative pneumonia.

Nursing home–acquired pneumonia

Common nursing home–acquired pneumonia pathogens include gram-negative bacilli, Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, anaerobes, and influenza viruses. Symptoms and signs are similar to those of pneumonia that occurs in other settings, except many elderly patients have less prominent changes in vital signs. Diagnosis is based on clinical presentation and chest x-ray, which is often not immediately available in nursing homes. Treatment is with antibiotics provided in the nursing home for less severe illness and in the hospital for more severe illness. Mortality is moderately high but may be due in part to comorbidities.

Nursing home–acquired pneumonia falls between community-acquired and hospital-acquired pneumonia in etiology and management. *Streptococcus pneumoniae* and gram-negative bacilli may be roughly equally responsible for most infections, though there is debate over whether gram-negative bacilli are pathogens or merely colonizers. *Haemophilus influenzae* and *Moraxella catarrhalis* are next most common; *Chlamydia*, *Mycoplasma*, and *Legionella* spp are rarely identified. Risk factors are common among debilitated nursing home residents; they include poor functional status, mood disorder, altered mental status, difficulty swallowing, immunosuppression, older age, use of tube feedings, influenza or other viral respiratory infections, conditions that predispose to bacteremia (eg, indwelling bladder catheter, pressure ulcers), and presence of a tracheostomy tube.

Symptoms and Signs

Symptoms often resemble those of community-acquired or hospital-acquired pneumonia but may be more subtle. Cough and altered mental status are common, as are nonspecific symptoms of anorexia, weakness, restlessness and agitation, falling, and incontinence. Subjective dyspnea occurs but is less common. Signs include diminished or absent responsiveness, fever, tachycardia, tachypnea, wheezes or crackles, and stertorous, wet breathing.

Diagnosis

- Clinical manifestations

- Chest x-ray
- Assessment of renal function and oxygenation

Diagnosis is based on clinical manifestations and chest x-ray. Because detection of physical changes may be delayed in a nursing home setting and because these patients are at greater risk of complications, evaluation for hypoxemia with pulse oximetry and for decreased intravascular volume with serum BUN and creatinine should also be done.

X-rays are often difficult to obtain in nursing home patients, so it may be necessary to transfer them to a hospital at least for initial evaluation. In some cases (eg, if clinical diagnosis is clear, if illness is mild, or if aggressive care is not the goal), treatment may be started without x-ray confirmation. It is thought that nursing home patients may initially lack a radiographic infiltrate, presumably because of the dehydration that commonly accompanies febrile pneumonia in the elderly or a blunted immune response, although the phenomenon is not proved to occur.

Prognosis

Mortality rate for patients requiring admission for treatment is 13 to 41%, whereas that for patients treated in the nursing home is 7 to 19%. Mortality rate exceeds 30% in patients with > 2 of the following findings:

- Respiratory rate > 30 breaths/min
- Heart rate > 125 beats/min
- Acute mental status change
- History of dementia

An alternative predictive index incorporates laboratory data. Physicians should follow all medical directives, because pneumonia is often a terminal event in debilitated nursing home patients.

Treatment

- Antibiotics given before hospitalization in patients being hospitalized

Few data are available to guide decisions about where treatment should take place. In general, patients should be hospitalized if they have ≥ 2 unstable vital signs and if the nursing home cannot administer acute care. Some nursing home patients are not candidates for aggressive treatment or hospital transfer under any circumstances. In patients who are to be hospitalized, one dose of antibiotics that are effective against *S. pneumoniae*, *H. influenzae*, and common gram-negative bacilli should be given before transfer; a common regimen is an oral antipneumococcal quinolone (eg, levofloxacin 750 mg once/day or moxifloxacin 400 mg once/day). Ceftriaxone, ertapenem, andampicillin/sulbactam (each as monotherapy) are alternatives.

Pneumonia in immunocompromised patients

is often caused by unusual pathogens. Symptoms and signs depend on the pathogen. Diagnosis is based on blood cultures and bronchoscopic sampling of respiratory secretions, sometimes with quantitative cultures. Treatment depends on the host defect and pathogen.

The potential pathogens in patients with compromised defenses are legion. However, respiratory symptoms and changes on chest x-rays in immunocompromised patients may be due to various processes other than infection, such as pulmonary hemorrhage, pulmonary edema, radiation injury, pulmonary toxicity due to cytotoxic drugs, and tumor infiltrates.

Symptoms and Signs

Symptoms and signs may be the same as those found with community-acquired or hospital-acquired pneumonia in immunocompetent patients, though immunocompromised patients may have no fever or respiratory signs and are less likely to have purulent sputum if they are neutropenic. In some patients, the only sign is fever.

Diagnosis

- Chest x-ray
- Assessment of oxygenation
- Induction or bronchoscopy to obtain sputum
- Blood cultures
- Pathogens predicted based on symptoms, x-ray changes, and type of immunodeficiency

An immunocompromised patient with respiratory symptoms, signs, or fever should undergo chest x-ray and assessment of oxygenation (usually by pulse oximetry). If an infiltrate is present, diagnostic studies should include sputum Gram stain and culture and blood cultures. Chest x-ray may be normal in *Pneumocystis jirovecii* pneumonia, but hypoxia is usually present. Optimally, a firm diagnosis is made with induced sputum, bronchoscopy, or both, especially in patients with chronic pneumonia, atypical presentation, severe defects in immune function, or failure to respond to broad-spectrum antibiotics.

Likely pathogens can often be predicted based on symptoms, x-ray changes, and the type of immunodeficiency. In patients with acute symptoms, likely diagnoses are bacterial infection, hemorrhage, pulmonary edema, a leukocyte agglutinin reaction, and pulmonary emboli. A subacute or chronic presentation is more suggestive of a fungal or mycobacterial infection, an opportunistic viral infection, *P. jirovecii* pneumonia, tumor, a cytotoxic drug reaction, or radiation injury.

X-rays showing localized consolidation usually indicate an infection involving bacteria, mycobacteria, fungi, or *Nocardia* sp. A diffuse interstitial pattern is more likely to represent a viral infection, *P. jirovecii*pneumonia, drug or radiation injury, or pulmonary edema. Diffuse nodular lesions suggest mycobacteria, *Nocardia* sp, fungi, or tumor. Cavitary disease suggests mycobacteria, *Nocardia* sp, fungi, or bacteria.

In organ or marrow transplantation recipients with bilateral interstitial pneumonia, the usual cause is cytomegalovirus, or the disease is idiopathic. A pleural-based consolidation is usually aspergillosis. In AIDS patients, bilateral pneumonia is usually *P. jirovecii* pneumonia. About 30% of patients with HIV infection have *P. jirovecii* pneumonia as the initial AIDS-defining diagnosis, and > 80% of AIDS patients have this infection at some time if prophylaxis is not given. Patients with HIV infection become vulnerable to *P. jirovecii* pneumonia when the $CD4^+$ helper cell count is < 200/μL.

Treatment

- Broad-spectrum antimicrobial therapy

In neutropenic patients, empiric treatment depends on the host defect, x-ray, and severity of illness. Generally, broad-spectrum drugs are needed to cover gram-negative bacilli, *Staphylococcus aureus*, and anaerobes, as for hospital-acquired pneumonia. If patients with conditions other than HIV do not improve with 5 days of antibiotic therapy, antifungal therapy is frequently added empirically.

Prevention

Therapies to enhance immune system function are indicated for the prevention of pneumonia in immunocompromised patients. For example, patients with chemotherapy-induced neutropenia should receive granulocyte-colony stimulating factor (G-CSF, or filgrastim), and patients with hypogammaglobulinemia due to an inherited or acquired disease (eg, multiple myeloma, leukemia) should receive IV immune globulin.

Patients with HIV and CD4+ helper cell count < 200/μL should receive daily prophylactic therapy with trimethoprim/sulfamethoxazole or other appropriate therapy.

Vaccination is also important in these patients. For example, patients at risk of pneumonia with encapsulated bacteria (eg, hypogammaglobulinemia, asplenia) should receive vaccinations again pneumococcus and *H. influenzae*.

PNEUMOCYSTIS JIROVECII PNEUMONIA

P. jirovecii is a common cause of pneumonia in immunosuppressed patients, especially in those infected with HIV and in those receiving systemic corticosteroids. Symptoms include fever, dyspnea, and dry cough. Diagnosis requires demonstration of the organism in an induced sputum specimen or bronchoscopic brushing. Treatment is with antibiotics, usually trimethoprim/sulfamethoxazole or dapsone/trimethoprim, clindamycin/primaquine, atovaquone, or pentamidine. Patients with Pao_2< 70 mm Hg receive systemic corticosteroids. Prognosis is generally good with timely treatment.

P. jirovecii is a ubiquitous organism transmitted by aerosol route and causes no disease in immunocompetent patients. Patients with HIV infection and CD4+ counts < 200/μL, organ transplant recipients, patients who have hematologic cancers, and patients taking corticosteroids are

at risk of developing *P. jirovecii* pneumonia. Most have fever, dyspnea, and a dry, nonproductive cough that evolves subacutely over several weeks (HIV infection) or acutely over several days (other causes of compromised cell-mediated immunity).

Diagnosis

- Chest x-ray
- Pulse oximetry
- Histopathologic confirmation

Patients should have chest x-ray and assessment of oxygenation by pulse oximetry. The chest x-ray characteristically shows diffuse, bilateral perihilar infiltrates, but 20 to 30% of patients have normal x-rays. However, hypoxemia is often present even when chest x-ray shows no infiltrate; this finding can be an important clue to diagnosis. When pulse oximetry is abnormal, ABGs are often obtained to show severity of hypoxemia (including an increase in the alveolar-arterial O_2 gradient). If obtained, pulmonary function tests show altered diffusing capacity (although this is rarely done as a diagnostic test).

Confirmation of diagnosis requires histopathologic demonstration of the organism with methenamine silver, Giemsa, Wright-Giemsa, modified Grocott, Weigert-Gram, or monoclonal antibody stain. Sputum specimens are usually obtained by induced sputum or bronchoscopy. Sensitivity ranges from 30 to 80% for induced sputum and is > 95% for bronchoscopy with bronchoalveolar lavage.

Prognosis

Overall mortality for *P. jirovecii*pneumonia in hospitalized patients is 15 to 20%. Risk factors for death may include previous history of *P. jirovecii*pneumonia, older age, and, in HIV-infected patients, CD4+ cell count <50/μL.

Treatment

- Trimethoprim/sulfamethoxazole
- Corticosteroids if Pa_{O_2}< 70 mm Hg

Treatment is with trimethoprim/sulfamethoxazole (TMP/SMX) 4 to 5 mg/kg IV or po tid for 14 to 21 days. Treatment can be started before diagnosis is confirmed because *P. jirovecii* cysts persist in the lungs for weeks. Adverse effects of treatment are more common among patients with AIDS and include rash, neutropenia, hepatitis, and fever. Alternative regimens are pentamidine 4 mg/kg IV once/day; atovaquone 750 mg po bid; TMP 5 mg/kg po qid with dapsone 100 mg po once/day; or clindamycin 300 to 900 mg IV q 6 to 8 h with primaquine base 15 to 30 mg/day po, also for 21 days. The major limitation of pentamidine is the high frequency of toxic adverse effects, including renal failure, hypotension, and hypoglycemia. Adjunctive therapy with corticosteroids is recommended for patients with a Pa_{O_2}< 70 mm Hg. The suggested regimen is prednisone 40 mg bid (or its equivalent) for the first 5 days, 40 mg once/day for the next 5 days (or 20 mg bid), and then 20 mg once/day for the duration of treatment.

Prevention

HIV-infected patients who have had *P. jirovecii* pneumonia or who have a CD4+ count < 200/μL should receive prophylaxis with TMP/SMX 80/400 mg once/day; if this regimen is not tolerated, dapsone100 mg po once/day or aerosolized pentamidine 300 mg once/month can be used. These prophylactic regimens are also probably indicated for non–HIV-infected patients at risk of *P. jirovecii*pneumonia.

Aspiration pneumonitis and pneumonia

Aspiration pneumonitis and pneumonia are caused by inhaling toxic substances, usually gastric contents, into the lungs. Chemical pneumonitis, bacterial pneumonia, or airway obstruction can occur. Symptoms include cough and dyspnea. Diagnosis is based on clinical presentation and chest x-ray findings. Treatment and prognosis differ by aspirated substance.

Aspiration can cause lung inflammation (chemical pneumonitis), infection (bacterial pneumonia or abscess), or airway obstruction. However, most episodes of aspiration cause minor symptoms or pneumonitis rather than infection or obstruction, and some patients aspirate with no sequelae. Risk

factors for aspiration include impaired cognition, impaired swallowing, vomiting, GI and respiratory devices and procedures (eg, nasogastric or endotracheal tube placement, dental work), and gastroesophageal reflux disease.

Pathophysiology

Chemical pneumonitis:

Multiple substances are directly toxic to the lungs or stimulate an inflammatory response when aspirated; gastric acid is the most common such aspirated substance, but others include petroleum products (particularly of low viscosity, such as petroleum jelly) and laxative oils (such as mineral, castor, and paraffin oil), all of which cause lipoid pneumonia. Aspirated gasoline and kerosene also cause a chemical pneumonitis.

Gastric contents cause damage mainly from gastric acid, although food and other ingested material (eg, activated charcoal as in treatment of overdose) are injurious in quantity. Gastric acid causes a chemical burn of the airways and lung leading to rapid bronchoconstriction, atelectasis, edema, and alveolar hemorrhage. Symptoms include acute dyspnea with cough that is sometimes productive of pink frothy sputum, tachypnea, tachycardia, fever, diffuse crackles, and wheezing. Chest x-ray shows diffuse infiltrates frequently but not exclusively in dependent segments, while pulse-oximetry and ABGs demonstrate hypoxemia. Treatment is supportive, often involving supplemental O_2 and mechanical ventilation. Antibiotics often are given to patients with witnessed or known gastric aspiration. The syndrome may resolve spontaneously, usually within a few days, or may progress to acute respiratory distress syndrome. Sometimes bacterial superinfection occurs.

Oil or petroleum jelly aspiration causes exogenous lipoid pneumonia, which is characterized histologically by chronic granulomatous inflammation with fibrosis. It is often asymptomatic and is detected incidentally on chest x-ray or may manifest with low-grade fever, gradual weight loss, and crackles. Chest x-ray findings vary; consolidation, cavitation, interstitial or nodular infiltrates, pleural effusion, and other changes may be slowly progressive. Treatment is avoidance of the toxic substance. Anecdotal reports suggest systemic corticosteroids may be beneficial.

Aspiration pneumonia:

Healthy people commonly aspirate small amounts of oral secretions, but normal defense mechanisms usually clear the inoculum without sequelae. Aspiration of larger amounts, or aspiration in a patient with impaired pulmonary defenses, often causes pneumonia and/or abscess. Elderly patients tend to aspirate because of conditions associated with aging that alter consciousness, such as sedative use and disorders (eg, neurologic disorders, weakness). Empyema also occasionally complicates aspiration.

Anaerobes often can be cultured from sputum, but it is unclear whether they are primary infecting organisms to which treatment should be directed or whether they are simply one of several organisms causing infection.

Risk factors for aspiration include

- Impaired cognition or level of consciousness
- Impaired swallowing (such as occurs after some strokes or other neurologic diseases)
- Vomiting
- GI devices and procedures (eg, nasogastric tube placement)
- Dental procedures
- Respiratory devices and procedures (eg, endotracheal tube placement)
- Gastroesophageal reflux disease

Symptoms and Signs

Symptoms and signs of pneumonia and abscess are similar and include chronic low-grade dyspnea, fever, weight loss, and cough productive of putrid, foul-tasting sputum. Patients may have signs of poor oral hygiene.

Diagnosis

Chest x-ray shows an infiltrate, frequently but not exclusively, in the dependent lung segments, ie, the superior or posterior basal segments of a lower lobe or the posterior segment of an upper lobe.

Treatment

Antibiotics, usually clindamycin

Abscess:

Treatment of lung abscess is with clindamycin 450 to 900 mg IV q 8 h followed by 300 mg po qid once fever and clinical symptoms subside. An alternative is a combination of penicillin (either penicillin G 1 to 2 million units q 4 to 6 h or amoxicillin 0.5 to 1 g po tid) plus either metronidazole 500 mg po tid, amoxicillin/clavulanate 875/125 mg po tid, or imipenem. Treatment is continued for 6 wk to 3 month.

Pneumonia:

Treatment of aspiration pneumonia can be with clindamycin, but other antibiotics with lower risk of adverse effects may be effective, because it is not clear that all the anaerobes cultured from the infection require specific treatment. Duration of treatment is usually 1 to 2 wk.

Equipment: class room, Harvey cardiopulmonary patient simulator, 6-channel ECG machine CARDIOLINE 100 L and Cardioline 200 + II S.

Lesson time: 2 hours

Plan

I. Organization moments (Greeting, roll-call, theme announce, aim of lesson, applicants motivation to study the topic).

II. Control of basic knowledges (The task source for self-knowledge skills tests from «KROK2» - additional materials, cheking workbooks)

II.1 Requirements for theoretical readiness of applicants to perform practical classes.

Requirements to knowledges:

- Definition of pneumonia
- Modern aspects of etiology and pathophysiology of pneumonia
- Classification of pneumonia
- Clinical manifestation of pneumonia
- Laboratory and instrumental investigation of pneumonia
- Carry out differential diagnosis of pneumonia
- Complications of pneumonia
- Treatment, rehabilitation of patients with pneumonia
- Prognosis and disability of patients with pneumonia

List of didactic units

- To get a detailed anamnesis
- To do physical examination of patient, to diagnose and to estimate changes in condition
- To make a plan of additional investigation and estimate it
- Justify and make a preliminary and clinical diagnoses of pneumonia based on severity of airflow limitation, complex evaluation of pneumonia a and make a group of patients.
- Basic principles of treatment pneumonia
- Estimation of clinical examination, CBC, blood tests, sputum tests, chest X-Ray, CT scan and etc.

II.2 Questions (MSQ, clinical cases) for basic knowledge examination of topic

1. A patient 25 y.o., after supercooling complains of frequent dry cough, rise of temperature to 38^{o}C, general weakness. Objectively: general condition is satisfactory. Right part of a chest - delay in the act of respiration, vocal tremor is unchanged. Percussively – reduction of a pulmonary sound in inferolateral part of chest, here during auscultation there’s coarse vesicular breathing, crepitation. RR 19 per min. Your preliminary diagnosis.

A. Pneumonia. +
B. Acute bronchitis.
C. Dry pleurisy.
D. Pleural effusion.
E. Lung abscess.

2. A patient with nosocomial pneumonia presents signs of collapse. Which of the following pneumonia complications is most likely to be accompanied by collapse?

A. Septic shock.+
B. Exudative plevritis.
C. Bronchial obstruction.
D. Toxic hepatitis.
E. Emphysema.

3. A 38 y.o. patient has been treated in a hospital. A fever of 39^0C, chest pain which is worsened by breathing, cough, brownish colored sputum appeared on the 7-th day of the treatment. Chest X- ray shows left lower lobe infiltrate. Which of the following is the treatment of choice for this patient?

A. Erythromycin.
B. Penicillin.
C. Cephalosporins of the III generation.+
D. Tetracycline.
E. Streptomycin.

4. A 56 year old woman has an acute onset of fever up to 39°C with chills, cough, and pain on respiration in the right side of her chest. On physical examination: HR - 90/min, BP- 95/60 mmHg, RR- 26/min. There is dullness over the right lung on percussion. On chest X-ray: infiltrate in the right middle lobe of the lung. What is the diagnosis?

A. Community-acquired lobar pneumonia of moderate severity. +
B. Community-acquired bronchopneumonia.
C. Acute plevritis.
D. Acute lung abscess.
E. Nosocomial lobar pneumonia.

5. A 55 y.o. male patient complains of weakness during 2 months, pain in the right side of the thorax, cough, blood-streaked sputum. On X-ray: intensive triangle shadow in the area of lower lobe that is connected to mediastinum. What is the most likely disorder in the lungs?

A. Central cancer of lungs.
B. Tuberculosis of lungs.
C. Bronchiectasia.
D. Pulmonary infarction. +
E. Pleuropneumonia.

6. A 22-year-old patient is a clerk. His working day runs in a conditioned room. In summer he was taken by an acute disease with the following symptoms: fever, dyspnea, dry cough, pleural pain, myalgia, arthralgia. Objectively: moist rales on the right, pleural friction rub. X-ray picture showed infiltration of the inferior lobe. In blood: WBC – $11*10^9$/l, banded neutrophils - 6%, segmented neutrophils - 70%, lymphocytes - 8%, ESR - 42 mm/h. What is the etiological factor of pneumonia?

A. Streptococcus.
B. Legionella.+
C. Mycoplasma.
D. Staphylococcus.
E. Pneumococcus.

7. A patient with community-acquired pneumonia of the lower lobe of a right lung, II category, an antibiotic therapy was prescribed: sheltered aminopenicilline (amoxiciliin/clavulan acid) preoraly. In 48 hours its inefficiency was detected. What medicine should be used in this case?

A. Fluoroquinolones of 3-4 generation.+
B. Cephalosporin of I generation.

C. Cephalosporin of III generation + macrolide.
D. Aminoglycoside.
E. Fluoroquinolon of 2 generation.

8. A 30 y.o. man presents with a history of recurrent pneumonias and a chronic cough production of foul smelling, pirulent sputum, ocassionally glood tinged, which is worse in the morning and on lying down. On physical examination, the patient appears chronically ill with clubbing of fingers, inspiratory rales at the base of lungs posteriorly. Most likely diagnosis:
A. Bronchoectasis. +
B. Chronic bronchitis.
C. Disseminated pulmonary tuberculosis.
D. Pulmonary neoplasm.
E. Chronic obstructive pulmonary disease.

9. At 66-year-old men was diagnosed: main disease – community-acquired pneumonia of the lower lobe of a right lung; concomitant diseases – Essential arterial hypertension III stage, 2 degree risk 4. Sequel of stroke in the left middle cerebral artery pool. Objective data - a clear conscience, T - 38,^{0} C, respiratory rate - 24/min., Pulse - 84 beats / min., rhythmic, BP - 150/90 mmHg, auscultation - moist fine rales lower right corner of the scapula. In which group should be classified this patient?
A. In I group
B. In II group
C. In III group +
D. In IV group
E. Data are insufficient.

10. Opportunistic protozoa Pneumocystis Carinii are the causative agent of pneumonia:
A. Community-acquired pneumonia.
B. Early nosocomial pneumonia.
C. Late nosocomial pneumonia.
D. Pneumonia due to aspiration.
E. In HIV-infected individuals. +

III. Proffesional skills formation (skills of patient`s management, treatment)
Professional algorithms: work with a patient (according to patients-students conversation algorithm).

During examination students must use next algorithm:

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Collecting data on patient complains, medical history, life history
5. Interpretation of clinical, laboratory and instrumental studies
6. Explanation for patient of next acting (hospitalization, workup)
7. End of conversation

Physical examination of patient with internal diseases

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Explanation of investigations are needed, taking agreement
5. Telling about possible negative feelings during investigation
6. Preparing to examination (clean warm hands, accurate nails, warm phonendoscope, screen if needed)
7. Examination (demonstration of clinical skills)
8. Interpretation of clinical, laboratory and instrumental studies
9. End of conversation

Telling to patient with internal diseases investigation results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of investigation results
5. Conversation with patient (comparing new and previous examination results, check if explanation is clear)
6. End of conversation

Planning and prognosing treatment results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of treatment
5. Conversation with patient (explanation of features taking pills, duration of taking drugs, possible side effects)
6. Check if explanation is clear
7. End of conversation

Telling treatment prognosis

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of expected treatment results
5. Conversation with patient (explanation of importance of life-long treatment, taking medications according to list, check if explanation is clear)
6. End of conversation

Task 1

1. Collecting complains, anamnesis, examination of patients with bronchial asthma
2. Identify clinical and instrumental symptoms
3. Make a syndrome based on symptoms
4. Identify the leading clinical syndrome
5. Assign laboratory and instrumental examination (CBC, urine analysis, blood tests, sputum tests, spirometry, bronchodilatation test, chest X-Ray, ECG, EchoCG and others)
6. Carry out differential diagnosis with lung abscess. lung cancer
7. Make a clinical diagnosis
8. Determine a degree of disability

Task 2

Prescribing different variants of treatment according to guidelines

Task 3

Work in Internet, work with thematic literature in department library room.
Student must fill patient examination protocol (example is added).

Control materials for final part of the lesson:

The cases for self-control with standard answers.

1. 4 days ago a 32-year-old patient caught a cold: he presented with sore throat, fatigue. The next morning he felt worse, developed dry cough, body temperature rose up to 38,2^{o}C, there appeared muco-purulent expectoration. Auscultation revealed weakening of vesicular breathing below the angle of the right scapula, fine sonorous and sibilant rales. What is the most likely diagnosis?
A. Focal right-sided pneumonia

B. Bronchial asthma
C . Acute bronchitis
D. Pulmonary carcinoma
E . Pulmonary gangrene
2. Male 68 y.o. adressed to a family doctor due to paroxysmal cough with little quantity of "rusty" sputum, pain in right side of chest, associated with deep breathing and coughing. Suffering from insulin-dependent diabetes. OBJECTIVE: t - 39,2 °C, RR - 24 / min., Ps - 114 bpm, BP - 110/70 mmHg The skin is dry, cheeks hyperemia. During auscultation in the lower part of right lung - moist rales. What should be the tactics of family doctor?
A. To prescribe outpatient treatment
B. Hospitalization in therapeutic department
C. Hospitalization in intensive care unit
D. Hospitalization in the endocrinology department
E. Direct to out hospital department for examination
3. Male 38 years, complains of paroxysmal cough with a little "rusty" sputum, pain in right side of chest, associated with deep breathing and coughing. These symptoms appeared after overcooling. Objectively: temperature - 39,2 °C, RR - 22 / min, Pulse - 114 bpm, BP -110/70 mmHg. Auscultation: in the lower part of right lung - moist sonorous rales. What is the pathogen most likely caused this disease?
A. Pneumococcus
B. Staphylococcus
C. Enterococci
D. Mycoplasma
E. Klebsiella
4. Patient 65 y.o. complains of breathlessness, cough with red foam sputum, dyspnea, fear of death. Objective: orthopnea. Pale skin, acrocyanosis, cold clammy sweat. Breathing harsh, a lower-back parts on both lungs small-bubbling moist rales. RR - 40 / min. Heart sound are deaf, at apex – gallop rhythm. What is the most likely previous diagnosis?
A. Lobar pneumonia
B. Pulmonary edema
C. Infarction - pneumonia
D. Pulmonary embolism
E. Acute severe bronchial asthma
5. A 56-year-old patient complains of having persistent chest pain on the right for the last 2 months. The pain is not associated with respiration. He also complains of cough with blood-streaked sputum, weakness, decreased performance, fatigue. Chest X-ray shows a round shade of 4x6 cm connected to the root of the lung in the lower part of the right lung. What is the most likely diagnosis?
A Tuberculoma
B Metastasis
C Lung abscess
D Pneumonia
E Peripheral lung cancer
6. A 22-year-old patient is a clerk. His working day runs in a conditioned room. In summer he was taken by an acute disease with the following symptoms: fever, dyspnea, dry cough, pleural pain, myalgia, arthralgia. Objectively: moist rales on the right, pleural friction rub. X-ray picture showed infiltration of the inferior lobe. In blood: WBC – $11x10^9$/l, banded neutrophils - 6%, segmented neutrophils - 70%, lymphocytes - 8%, ESR - 42 mm/h. What is the etiological factor of pneumonia?
A Legionella
B Mycoplasm
C Streptococcus
D Staphylococcus

E Pneumococcus

7. A 26-year-old patient with left lower lobe pneumonia experiences an acute chest pain on the left during coughing. Objectively: diffuse cyanosis, extension of the left side of chest. Percussion reveals high tympanitis. Auscultation reveals no respiratory murmurs above the left side of chest. There is a deviation of the right cardiac border towards the midclavicular line. What examination will be the most informative?

A Bronchoscopy
B Chest X-Ray
C Bronchography
D Pneumotachometry
E Spirography

8. The patient is 67 y.o. complaining of shortness of breath, chest pain, general weakness. Sick for 5 months. OBJECTIVE: T - 37,3 °C, Ps- 96 bpm. Above right lung voice tremor is not defined, dull percussion sound, breathing is not listening. In sputum - impurities of blood that diffuse mixed with mucus. What is the most likely diagnosis?

A. Focal tuberculosis
B. Lobar pneumonia
C. Bronchiectasis
D. Lung cancer
E. Pleural effusion

9. Patient on 4 –th day after surgery due to cystoma of right ovary noticed the suddenly appeared pain in the right half of the chest with a discharge of pink colored sputum, fever up to 37,7 °C. The examination of the lungs revealed dullness of pulmonary sound and few moist rales in the lower part of right lung. What complication is most likely?

A. Pneumonia
B. Pneumothorax
C. Pulmonary infarction
D. Lung abscess
E. pleural effusion

10. A 56 year old woman has an acute onset of fever up to 39ºC with chills, cough, and pain on respiration in the right side of her chest. On physical examination: HR – 90 bpm, BP-95/60 mmHg, RR- 26/min. There is dullness over the right lung on percussion. On X-ray: infiltrate in the right middle lobe of the lung. What is the diagnosis?

A Nosocomial lobar pneumonia
B Community-acquired bronchopneumonia
C Acute pleuritis
D Acute lung abscess
E Community-acquired lobar pneumonia of moderate severity

Standard answers: 1-A, 2-B, 3-A, 4-B, 5-E, 6-A, 7-B, 8-D, 9-C, 10-E.

IV. Making conclusions, telling final marks, tasks for the next lesson

Literature list:

- Basic literature source:

1. Harrison's Manual in Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 1245 p.
2. Harrison's Principles of Internal Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 3528 p.

- Additional literature source:

1. Rider AC, Frazee BW. Community-Acquired Pneumonia. Emerg Med Clin North Am. 2018;36(4):665-683.

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European male of 68 years old.

COMPLAINTS: fever, shaking, chills and malaise along with the productive cough

HISTORY: Mr. B. is a 68 year old man who developed a harsh, productive cough four days prior to being seen by a physician. The sputum is yellow. He developed a fever, shaking, chills and malaise along with the cough.

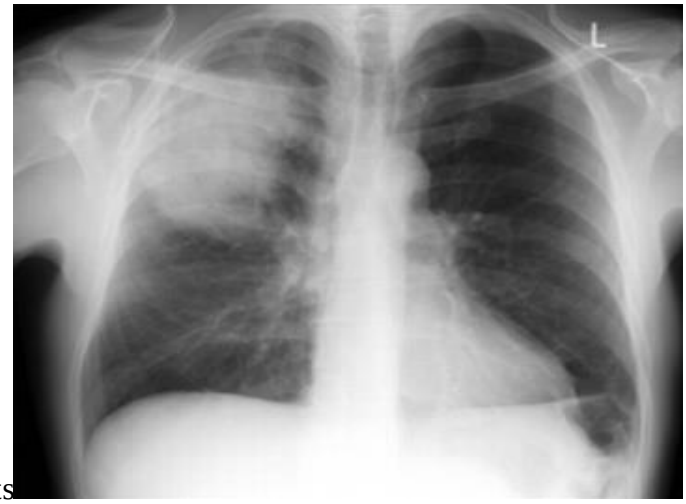
PHYSICAL EXAMINATION: The patient is an elderly man who appears tired haggard. His complexion is sallow. He coughs continuously. Vital signs are as follows: blood pressure 138/85, apical heart rate 112/minute and regular, respiratory rate 20/minute and somewhat labored, temperature 38˚C. Both lungs are resonant by percussion with one exception: the right mid-anterior and right mid-lateral lung fields are dull. Auscultation reveals bilateral diminished vesicular breath sounds. Bronchial breath sounds, rhonchi and late inspiratory crackles (are heard) in the area of the right mid-anterior and right mid-lateral lung fields. The remainder of the lung fields is clear. Percussion and auscultation of the heart reveals no significant abnormality. Abdomen is not painful. No peripheral edema.

Diagnosis:

Community-acquired polysegmental right sided pneumonia

Examination plan:

1. Cell blood count,
2. blood biochemistry: creatinine, urea
3. coagulation test,



4. liver function tests
5. Chest X-Ray
6. ECG
7. Sputum test

8. Chest X-Ray

CBC: WBC-17 G/l, neutrophils-80%. ESR 67%

Another blood tests, ECG without pathological signs

Treatment plan:

1. Amoxicillin 500 mg orally 3 times per day, 10 days
2. Ambroxol 15 mg orally 2 times per days, 5 days
3. Paracetamol 500 mg 1 time per day, 5 days

Practical lesson № 15

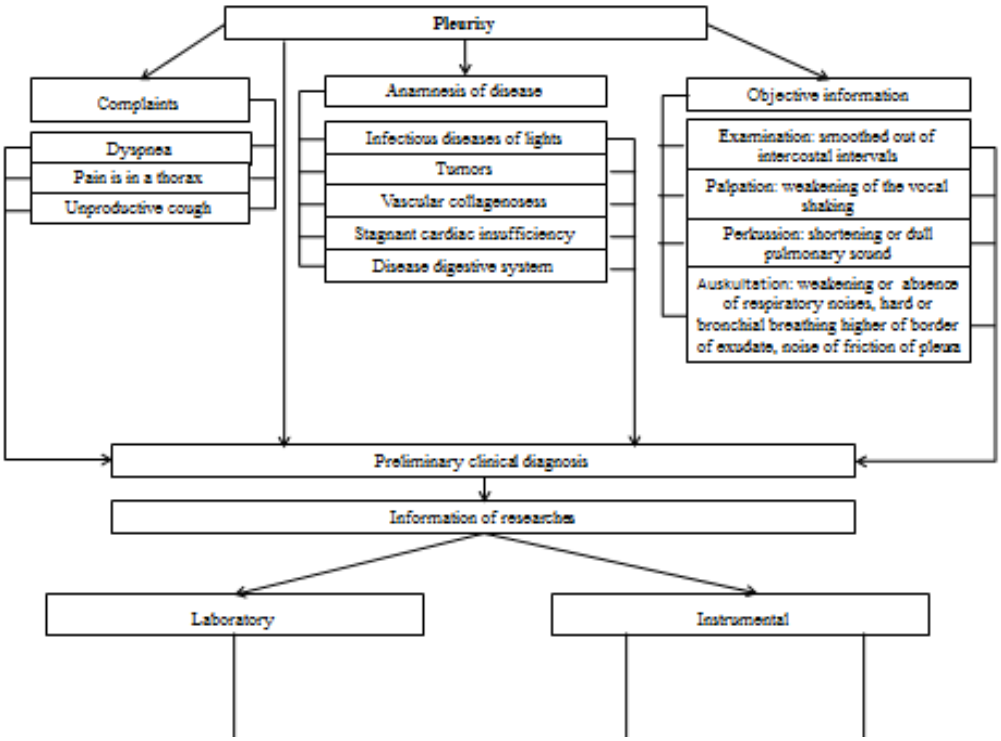
Theme: Pleuritis and pleural effusion

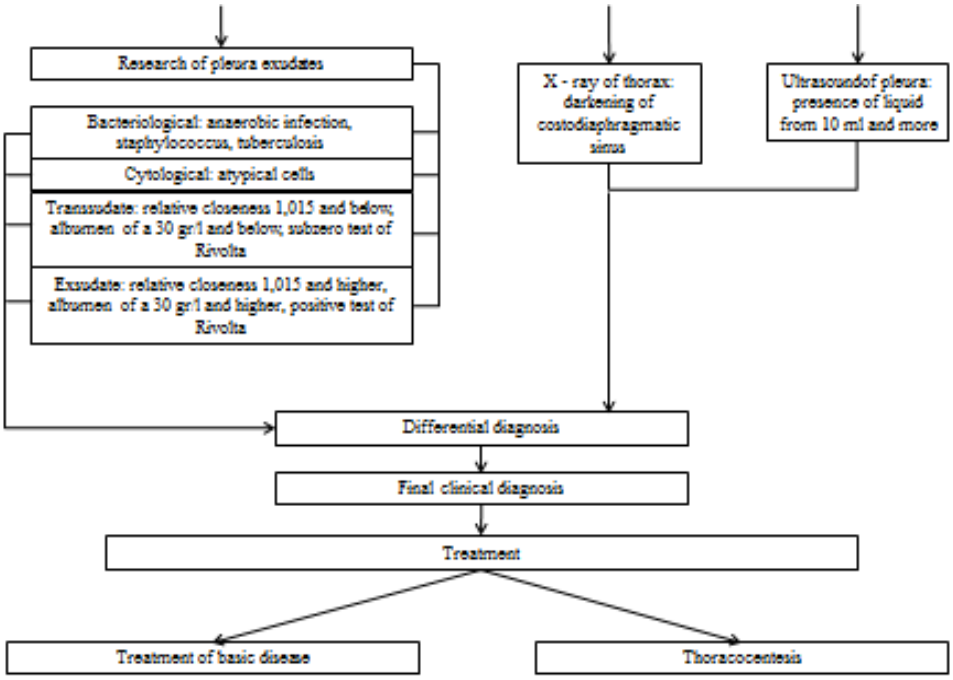
Object: To teach applicants to master the method of examination of patients with respiratory diseases with the selection of the main pulmonological syndromes. To study probable etiological factors, pathogenesis of pleuritis and pleural effusion, their main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis and efficiency of patients.

Basic concepts:

№	Term	Definition
1	Transudate	collection of fluid that has a relatively low specific gravity and protein concentration (fluid total protein – 2.5 g/dL or less)
2	Exudate	fluid collections with a density greater than 1.016 and a protein content greater than 2.5 g/dL.
3	Pneumothorax	abnormal collection of air in the pleural space
4	Hydrothorax	noninflammatory collection of serous fluid within the pleural cavities
5	Chylothorax	abnormal accumulation of chyle, a type of lipid-rich lymph in the pleural space
	Hemothorax	accumulation of blood within the pleural cavity
	Empyema	condition in which pus gathers in the pleural space

5. Content of practical lesson





Differential diagnosis of «chest pain» syndrome

Chest pain

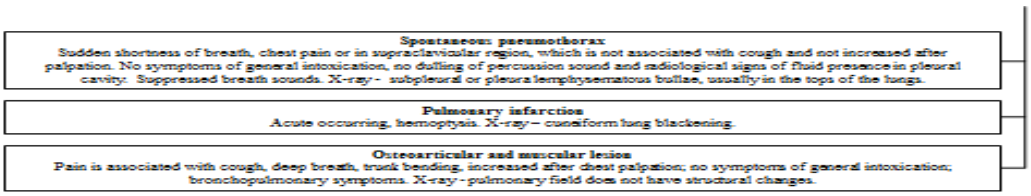
Parapneumonic effusion and pleural empyema
In the medical history there are bacterial lung disease, surgery, chest injuries, perforation of the esophagus, subdiafragmal infection. Chest pain, increased with deep breathing, trunk bending; persistent, recurrent fever, weight loss, symptoms of general intoxication. Neutrophilic leukocytosis, accelerated erythrocyte sedimentation rate, increased C-reactive protein. Focal dullness of percussion sound. X-ray - focal accumulation of fluid in the pleural cavity

Fibrinous dry pleuritis
Chest pain, increased after cough, deep breathing, trunk bending, weakness, low-grade pyrexia. Pain in the hypochondrium, radiating to shoulder, belching, nausea, vomiting, stiffness in the muscles of the anterior abdominal wall (with diaphragmatic pleurisy). Rigidity upper pectorals, trapezius muscles, muscles of the anterior abdominal wall. Palpatory vibration of pleural friction in inflammation area. Auscultation - pleural friction rub. X-ray- pleura thickening, the presence of pleural adhesions.

Pleural lesion in case of cancer
At risk - smokers, patients with breast cancer, ovarian cancer, gastrointestinal tract. Symptoms of general intoxication, fatigue, weight loss. Dullness of percussion ("stone" stupidity) sound, easing breathing. X-ray - accumulation of fluid in the pleural cavity. Pleural puncture with aspiration and biopsy - pleural effusion of hemorrhagic nature, which contains abnormal cells.

Perifocal tuberculosis pleuritis
It is possible in tuberculosis patients in case of subpleural location of main focus. Relapsing course. Pleural serosal effusion with large amount of white blood cells. X-ray - pleural adhesions, focal (encapsulation) liquid accumulation in pleural cavity, presence of main lesion focus. Positive tuberculosis tests.

Exudative pleuritis
Shortness of breath, involuntary body posture, cyanosis of lips, swelling of the neck veins, delay of affected side in the act of breathing, suppressed breath sounds, focal dullness of percussion sound. X-ray - blackening with horizontal fluid level. Pleural puncture and aspiration - fluid (exudate/transudate) of various morphological structures.



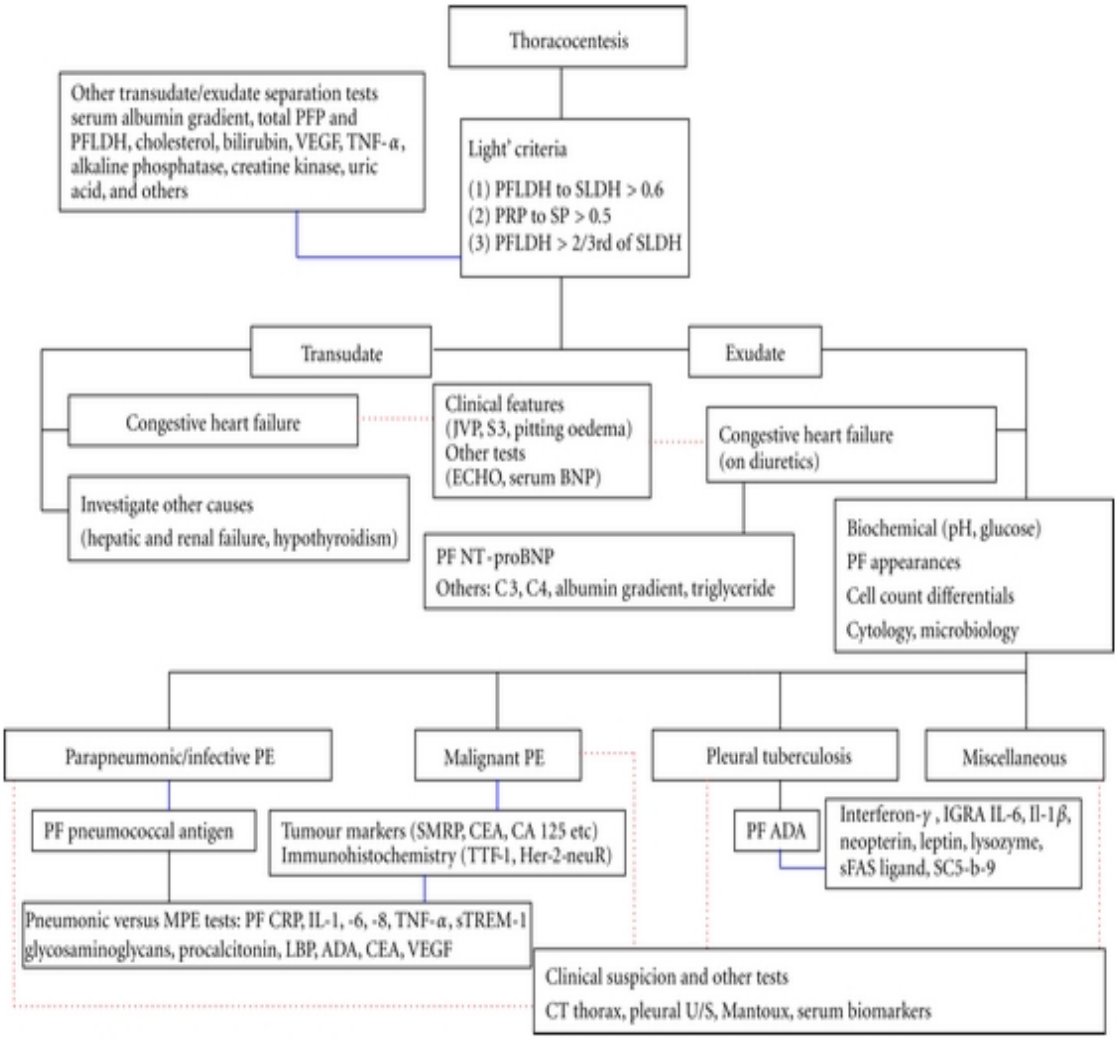


Figure 1: Recommended algorithm for investigation of pleural effusion.

The use of Light's criteria is recommended when a thoracocentesis revealed a protein level between 25 and 35 g/L to narrow down the differential diagnosis by determining whether a pleural effusion is transudative or exudative. NT-proBNP should be measured when a suspected cardiac effusion meets the exudative criteria. Determining causes of an exudative effusion is more challenging, and routine test, including biochemical measurement (i.e., pH and glucose), differential cell counts, cytology, and routine microbiology test are diagnostically useful. Pleural fluid pneumococcal antigen has been shown to be superior than urinary antigen to identify bacterial-induced pleural effusion. Tumour marker such as SMRP has a good diagnostic value to diagnose mesothelioma, however, the diagnostic utility of other tumour markers remains limited. Immunocytochemical evaluation of pleural fluid specimen is helpful in labelling different tumour markers. Other biological markers to differentiate parapneumonic/infective and malignant effusion remain elusive, expensive, and not widely available. Testing of pleural fluid ADA is an inexpensive and efficacious method for diagnosing tuberculous effusion, regardless of the patient's immune status. Other tuberculosis-related inflammatory markers are available but are not superior to the latter. (PF: pleural fluid, black continuous line: strongly recommended and routinely practiced, blue continuous line: not strongly recommended and not routinely practiced, red dotted line: complementary diagnosis with other nonpleural tests.)

Equipment: class room, Harvey cardiopulmonary patient simulator, 6-channel ECG machine CARDIOLINE 100 L and Cardioline 200 + II S

Lesson time: 2 hours

Plan

I. Organization moments (Greeting, head count, theme announce, aim of lesson, students motivation for preparing for lesson).
II. Control of basic knowledges (The task source for self-knowledge skills tests from «KROK2» - additional materials, cheking workbooks)

II.1 Requirements for theoretical readiness of students to perform practical classes.

Requirements to knowledges:
- Definition of pleuritis and pleural effusion
- Modern aspects of etiology and pathophysiology of pleuritis and pleural effusion
- Classification of pleuritis and pleural effusion
- Clinical manifestation of pleuritis and pleural effusion
- Laboratory and instrumental investigation of pleuritis and pleural effusion
- Carry out differential diagnosis of pleuritis and pleural effusion
- Complications of pleuritis and pleural effusion
- Treatment, rehabilitation of patients with pleuritis and pleural effusion
- Prognosis and disability of patients with pleuritis and pleural effusion

List of didactic units
- To get a detailed anamnesis
- To do physical examination of patient, to diagnose and to estimate changes in condition
- To make a plan of additional investigation and estimate it
- Justify and make a preliminary and clinical diagnoses of pleuritis and pleural effusion based on severity of airflow limitation, complex evaluation of pleuritis and pleural effusion and make a group of patients.
- Basic principles of treatment pleuritis and pleural effusion
- Estimation of clinical examination, CBC, blood tests, sputum tests, chest X-Ray and etc.

- Indications to pleurocentesis and drainage of pleural cavity.

II.2 Questions (MSQ, clinical cases) for basic knowledge examination of topic

1. A 26 year old man was admitted to the hospital because of stabbing back pain on inspiration and dyspnea. Examination results: T of 37ºC, RR 24/min, HR 92 bpm, vesicular breath sounds. There is a dry, grating, low-pitched sound heard on both expiration and inspiration phase in the left inferior lateral part of the chest. What is the most likely diagnosis?
A. Acute fibrinous Plevritis. +
B. Myocarditis.
C. Pneumonia.
D. Acute bronchitis.
E. Pneumothorax.
2. Examination of a 22 year old man suffering from polyarthralgia and high fever revealed right-sided exudative plevritis. X-ray picture showed a homogenous shadow below the IV rib on the right. In the II segment there were single dense focal shadows. Mantoux test with 2 TU resulted in formation of a papula 16 mm large. Pleural liquid has increased protein concentration, Rivalt's reaction is positive, there was also increased number of leukocytes with prevailing lymphocytes. What is the most probable etiology of plevritis?
A. Tuberculous.+
B. Cancerous.
C. Staphylococcal.
D. Viral.
E. Autoimmune.
3. A 52 y.o. male patient has become ill gradually. There is pain in the left side of the thorax during 2 weeks, elevation of temperature till 38-39 C. On examination: left chest side – delay during breathing movement; no voice tremor over the left lung. Dullness that is more intensive in lower parts of this lung. Right heart border is deviated outside. Sharply weakened breathing over the left lung, no rales. Heart sounds are muffled, tachycardia. What is the most probable diagnosis?
A. Exudative plevritis. +
B. Spotaneous pneumothorax.
C. Atelectasis of lung.
D. Cirrhotic tuberculosis.
E. Infarction-pneumonia.
4. A 26-year-old male patient complains of piercing pain during breathing, cough, dyspnea. Objectively: 37,3 ºC respiration rate - 19/min, heart rate = Ps- 92/min; AP- 120/80 mm Hg. Vesicular breathing. In the infero-lateral parts of chest
auscultation in both inspiration and expiration phase revealed noise that was getting stronger at phonendoscope pressing and can be still heard after cough. ECG showed no pathological changes. What is the most likely diagnosis?
A. Acute plevritis.+
B. Intercostal neuralgia.
C. Subcutaneous emphysema.
D. Spontaneous pneumothorax.
E. Pericarditis sicca.
5. In a sample obtained by puncture of pleural cavity defined by: relative density - 1.012, protein - 27 g / l, the Rivalt reaction - negative, glucose - 5.25 mmol / L, WBC - 3-5 in f/v, erythrocytes - 2-3 in f/v. Determine the nature of the liquid:
A. exudate
B. transudate +
C. chylous fluid
D. hemorrhagic fluid

E. purulent fluid

6. The patient is 32 years old, complaining of dry cough, pain in the right side of the chest, increasing at breathing and coughing, sweating at night. Pain decreases in supine position on the right side. Six days ago was a trauma of the chest. Objectively - t0 - 37,1^0 C, RR - 18/min., Pulse – 84 bpm., Rhythmic, BP - 120/80 mmHg. The chest of the normal form, the right side a little delayed during breathing. Percussion over both lung fields – clear lung sound. Vesicular breathing, at the inferio-lateral part of right lung during inhalation and exhalation auscultated low-pitched sound, that was getting stronger at phonendoscope pressing. Chest X-ray and an electrocardiogram revealed no pathology. The most likely diagnosis is:

A spontaneous pneumothorax

B. pulmonary embolism

C. Community-acquired pneumonia

D. fibrinous pleurisy +

E. pleural effusion

7. The patient is 42 years old, addressed to the clinic with complaints of cough, pain in his right side during breathing, weakness, increased T to 37.8^{0}C. During the initial inspection revealed: RR – 21bpm, dullness on the right lower corner of the scapula, auscultation - crepitation. On chest X-ray - infiltrate in the lower lobe of the right lung. Primary diagnosis: Basic disease: community-acquired low-lobe right sided pneumonia II clinical group, mild severity, LI (lung insufficiency) I. Associated disease: coronary artery disease, stable angina FC I, CH I. The patient was at home, took Zinacef (Cefuroxime) orally. After 5 days noticed increased dyspnea. Objectively: T - 37,5^0 C, from the right under scapula: severe weakening of voice trembling, dull percussion sound, vesicular breath sharply reduced. What complication can be assumed:

A parapneumonic fibrinous pleurisy

B. parapneumonic pleural effusion +

C. infectious lung destruction

D. acute myocarditis

E. bronchial obstruction

8. A patient 51 years old, complaining of dyspnea, increasing in a horizontal position, especially on the left side. Objective: The patient in forced sitting position, acrocyanosis, RR - 27/min., Heart rate - 110 beats / min., Arrhythmias, blood pressure - 140/90 mmHg. Over the right half of the chest voice trembling sharply weakened, dull percussion sound, auscultation - vesicular breath sharply reduced. On chest X-ray - left homogeneous shadow to level II with the upper edge slash, mediastinal organs are shifted to the right. The method of choice for the treatment in this case is:

A treatment-diagnostic pleural puncture +

B. parenteral therapy with corticosteroids

C. parenteral antibiotic therapy

D. parenteral diuretic therapy

E. parenteral therapy NSAIDs

9. The optimal amount of pleural effusion was evacuated during the one-off treatment of pleural puncture is:

A. 2000-2500 ml

B. 1000 ml

C. 1000-1500 ml +

D. 2500-3000 ml

E. 3000-3500 ml

10. Nonetiology treatment of fibrinosis pleurisy includes:

A. non-steroidal anti-inflammatory agents

B. Non-narcotic anticoughing drug

C. antihystamine drugs

D. tight bandaging of the chest

E. all of above +

III. Proffesional skills formation (skills of patient`s management, treatment)
Professional algorithms: work with a patient (according to patients-students conversation algorithm).

During examination students must use next algorithm:

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Collecting data on patient complains, medical history, life history
5. Interpretation of clinical, laboratory and instrumental studies
6. Explanation for patient of next acting (hospitalization, workup)
7. End of conversation

Physical examination of patient with internal diseases

10. Nice face, smiling
11. Gentle tone of speech
12. Greeting and acquaintance, interesting in patients, showing care and respect
13. Explanation of investigations are needed, taking agreement
14. Telling about possible negative feelings during investigation
15. Preparing to examination (clean warm hands, accurate nails, warm phonendoscope, screen if needed)
16. Examination (demonstration of clinical skills)
17. Interpretation of clinical, laboratory and instrumental studies
18. End of conversation

Telling to patient with internal diseases investigation results

7. Nice face, smiling
8. Gentle tone of speech
9. Greeting та acquaintance, interesting in patients, showing care and respect
10. Correct and understandable for patient explanation of investigation results
11. Conversation with patient (comparing new and previous examination results, check if explanation is clear)
12. End of conversation

Planning and prognosing treatment results

8. Nice face, smiling
9. Gentle tone of speech
10. Greeting and acquaintance, interesting in patients, showing care and respect
11. Correct and understandable for patient explanation of treatment
12. Conversation with patient (explanation of features taking pills, duration of taking drugs, possible side effects)
13. Check if explanation is clear
14. End of conversation

Telling treatment prognosis

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of expected treatment results
5. Conversation with patient (explanation of importance of life-long treatment, taking medications according to list, check if explanation is clear)
6. End of conversation

Task 1

1. Collecting complains, anamnesis, examination of patients with pleuritis and pleural effusion
2. Identify clinical and instrumental symptoms
3. Make a syndrome based on symptoms
4. Identify the leading clinical syndrome
5. Assign laboratory and instrumental examination (CBC, urine analysis, blood tests, sputum tests, analysis of pleural fluid, chest X-Ray, CT scan, ECG, EchoCG and others)
6. Carry out differential diagnosis between different types of pleural effusion
7. Make a clinical diagnosis
8. Determine a degree of disability

Task 2

Prescribing different variants of treatment according to guidelines

Task 3

Work in Internet, work with thematic literature in department library room.
Student must fill patient examination protocol (example is added).

Control materials for final part of the lesson:

The cases for self-control with standard answers.

1. A 29-year-old female patient complains of dyspnea, heaviness and chest pain on the right, body temperature rise up to 37,2ºC. The disease is associated with a chest trauma received 4 days ago. Objectively: skin is pale and moist. Ps- 90 bpm, regular. Palpation reveals a dull sound on the right, auscultation reveals significantly weakened vesicular breathing. In blood: RBCs - $2,8x10^{12}$/l, colour index - 0,9, Hb- 100 g/l, WBCs - $8,0x10^{9}$/l, ESR - 17 mm/h. What results of diagnostic puncture of the pleural cavity can be expected?

A Haemorrhagic punctate
B Chylous liquid
C Exudate
D Transudate
E Purulent punctate

2. A 52 y.o. male patient has become ill gradually. There is pain in the left side of the thorax during 2 weeks, elevation of temperature till $38\text{-}39^{0}$C. On examination: left chest side falls behind in breathing movement no voice tremor over the left lung. Dullness that is more intensive in lower parts of this lung. Right heart border is deviated outside. Sharply weakened breathing over the left lung, no rales. Heart sounds are muffled, tachycardia. What is the most probable diagnosis?

A Infarction-pneumonia
B Spotaneous pneumothorax
C Atelectasis of lung
D Cirrhotic tuberculosis
E Exudative plevritis

3. A 26-year-old male patient complains of piercing pain during breathing, cough, dyspnea. Objectively: tº- 37,3ºC, respiration rate - 19/min, heart rate=Ps – 92bpm; AP- 120/80 mm Hg. Vesicular respiration. In the inferolateral parts of chest auscultation in both inspiration and expiration phase revealed noise that was getting stronger at phonendoscope pressing and can be still heard after cough. ECG showed no pathological changes. What is the most likely diagnosis?

A Spontaneous pneumothorax
B Intercostal neuralgia
C Subcutaneous emphysema

D Acute plevritis
E Pericarditis sicca
4. Examination of a 22 year old man suffering from polyarthralgia and high fever revealed right-sided exudative plevritis. X-ray picture showed a homogenous shadow below the IV rib on the right. In the II segment there were single dense focal shadows. Mantoux test with 2 TU resulted in formation of a papula 16 mm large. Pleural liquid has increased protein concentration, Rivalt's reaction is positive, there was also increased number of leukocytes with prevailing lymphocytes. What is the most probable etiology of pleurisy?
A Staphylococcal
B Cancerous
C Tuberculosis
D Viral
E Autoimmune
5. A patient complains about severe dyspnea that is getting worse during physical activity. Presentations appeared suddenly 2 hours ago at work: acute chest pain on the left, cough. The pain was abating, but dyspnea, dizziness, pallor, cold sweat and cyanosis were progressing. Vesicular respiration is weakened in the left lung, X-ray picture shows a shadow on the left lung. What pathology might be suspected?
A. Pleuritis
B. Pulmonary infarction
C. Pulmonary abscess
D. Left-sided pneumonia
E. Spontaneous left-sided pneumothorax

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

IV. Making conclusions, telling final marks, tasks for the next lesson

Literature list

- Basic literature source:

1. Harrison's Manual in Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 1245 p.
2. Harrison's Principles of Internal Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 3528 p.
3. BTS Pleural disease guideline 2022 – a quick reference guide

- Additional literature source:

1. Krishna R, Rudrappa M. Pleural Effusion. 2021 Aug 11. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–. PMID: 28846252.

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European male of 68 years old.

COMPLAINTS: fever, shaking, chills and malaise along with the productive cough

HISTORY: Mr. B. is a 68 year old man who developed a harsh, productive cough four days prior to being seen by a physician. The sputum is yellow. He developed a fever, shaking, chills and malaise along with the cough. One day ago he developed pain in his right chest that intensifies with inspiration.

PHYSICAL EXAMINATION: The patient is an elderly man who appears tired haggard. His complexion is sallow. Sitting in a chair, he leans to his right side, holding his right chest with his left arm. He coughs continuously. Vital signs are as follows: blood pressure 138/85, apical heart rate 112/minute and regular, respiratory rate 24/minute and somewhat labored, temperature 38˚C. Percussion: dull sound in the lower part of right lung. Bronchial breath sounds, rhonchi and late inspiratory crackles (are heard) in the area of the right lower lung fields. The remainder of the lung fields is clear. Percussion and auscultation of the heart reveals no significant abnormality. Abdomen is not painful. No peripheral edema.

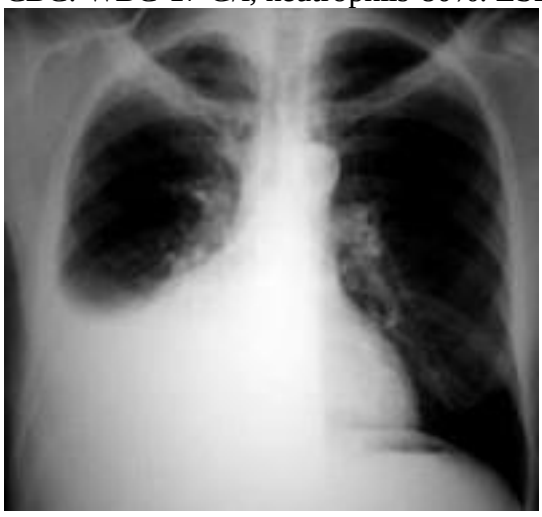
Diagnosis:

Community-acquired polysegmental right sided pneumonia, ride sided plevritis

Examination plan:

1. Cell blood count,
2. blood biochemistry: creatinine, urea
3. coagulation test,
4. liver function tests
5. Chest X-Ray
6. ECG
7. Sputum test

CBC: WBC-17 G/l, neutrophils-80%. ESR 67%



Chest X-Ray

Treatment plan:

1. Ceftriaxone 1.0 g i.v. 2 times per day, 10 days
2. Levofloxacine 500 mg once a day, 10 days
3. Ambroxol 15 mg orally 2 times per day
4. Paracetamol 500 mg 1 time per day
5. Sol. «Reosorbilact» 200 ml i.v. once a day
6. Sol. Torasemide 20 mg i.v. once a day

Practical lesson № 16

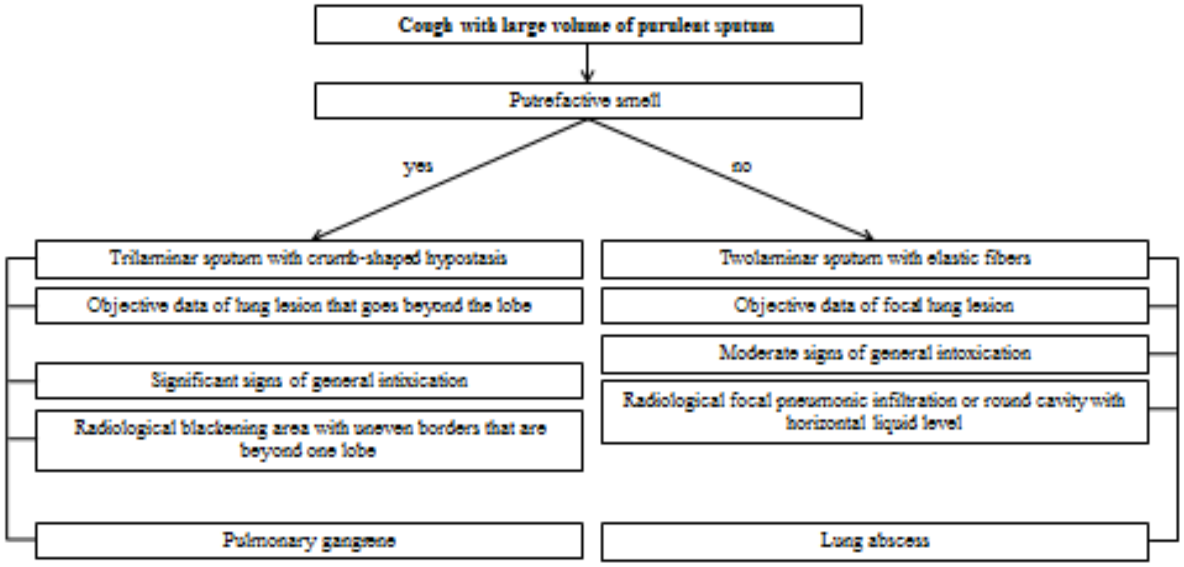
Theme: Infective destructive bronchopulmonary diseases

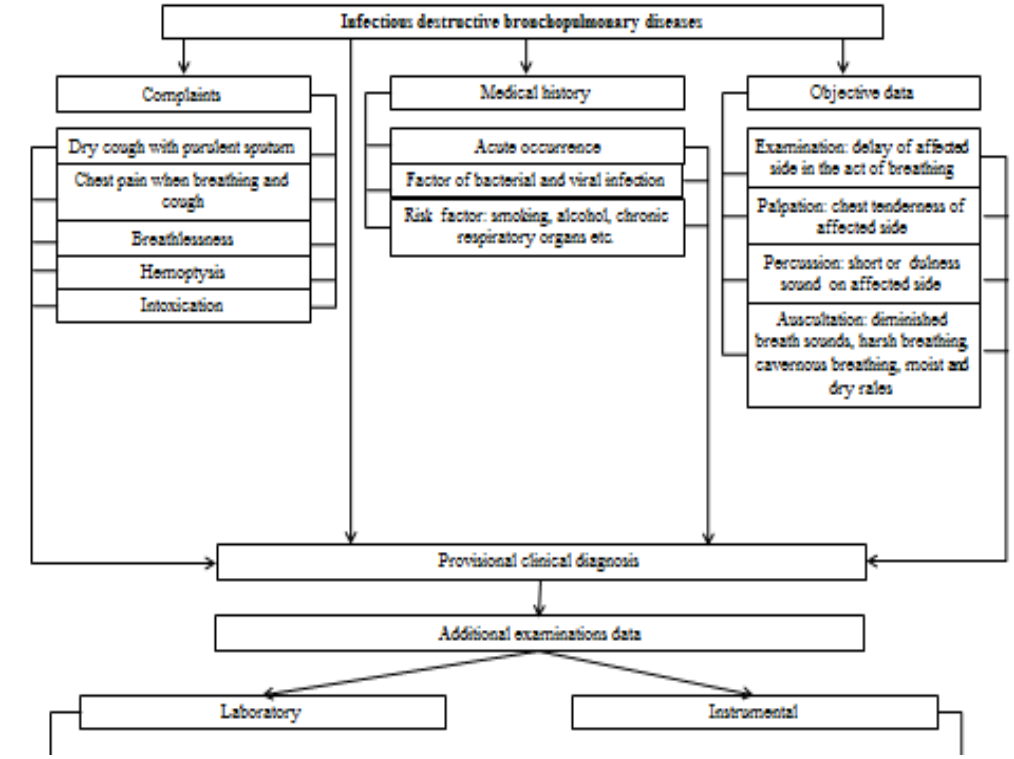
Object: To teach applicants to master the method of examination of patients with respiratory diseases with the selection of the main pulmonological syndromes. To study probable etiological factors, pathogenesis of chronic obstructive pulmonary diseases, their main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis and efficiency of patients.

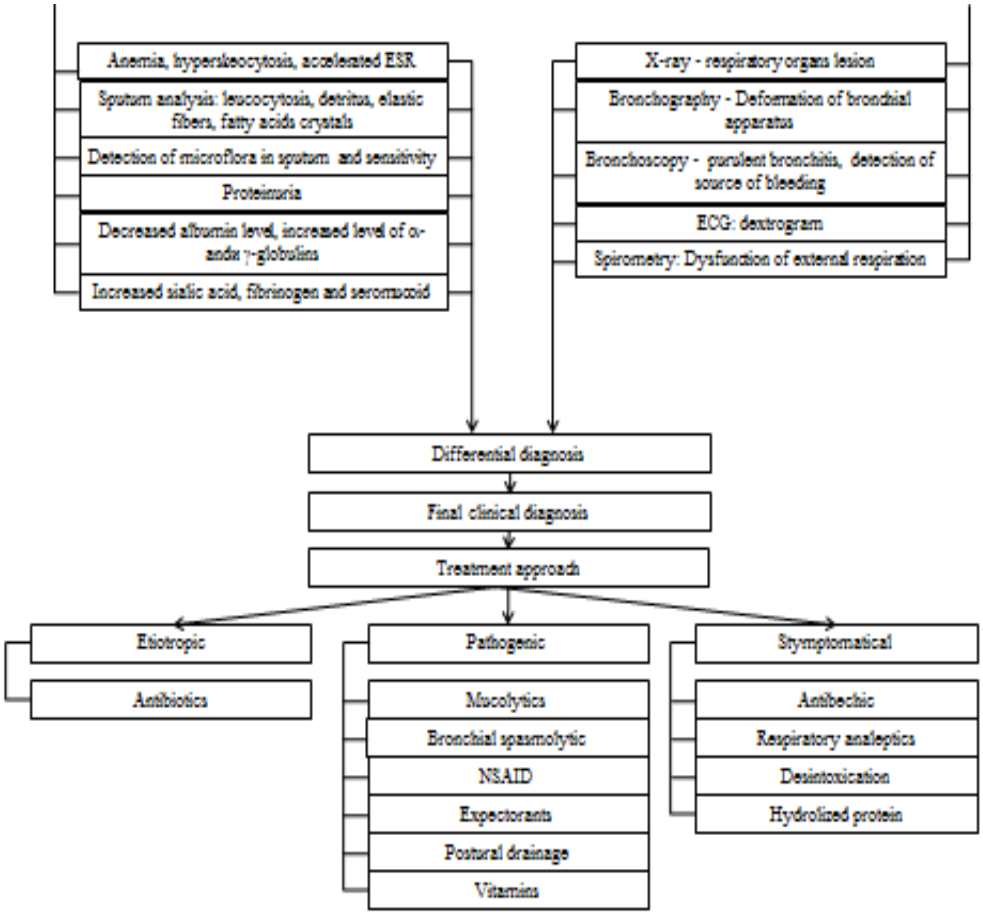
Basic concepts

№	Term	Definition
1	Lung abscess	is a necrotizing lung infection characterized by a pus-filled cavitary lesion.
2	Bronchiectasis	is dilation and destruction of larger bronchi caused by chronic infection and inflammation.

Differential diagnosis of «cough with large volume of purulent sputum» syndrome




Infectious destructive bronchopulmonary diseases
Complaints
Medical history
Objective data
Dry cough with purulent sputum
Chest pain when breathing and cough
Breathlessness
Hemoptysis
Intoxication
Acute occurrence
Factor of bacterial and viral infection
Risk factor: smoking, alcohol, chronic respiratory organs etc.
Examination: delay of affected side in the act of breathing
Palpation: chest tenderness of affected side
Percussion: short or dulness sound on affected side
Auscultation: diminished breath sounds, harsh breathing, cavernous breathing, moist and dry rales
Provisional clinical diagnosis
Additional examinations data
Laboratory
Instrumental


Anemia, hypersleocytosis, accelerated ESR
Sputum analysis: leucocytosis, detritus, elastic fibers, fatty acids crystals
Detection of microflora in sputum and sensitivity
Proteinuria
Decreased albumin level, increased level of α- and γ-globulins
Increased sialic acid, fibrinogen and seromucoid
X-ray - respiratory organs lesion
Bronchography - Deformation of bronchial apparatus
Bronchoscopy - purulent bronchitis, detection of source of bleeding
ECG: dextrogram
Spirometry: Dysfunction of external respiration
Differential diagnosis
Final clinical diagnosis
Treatment approach
Etiotropic
Antibiotics
Pathogenic
Mucolytics
Bronchial spasmolytic
NSAID
Expectorants
Postural drainage
Vitamins
Stymptomatical
Antibechic
Respiratory analeptics
Desintoxication
Hydrolized protein

Bronchiectasis

is dilation and destruction of larger bronchi caused by chronic infection and inflammation. Common causes are cystic fibrosis, immune defects, and recurrent infections, though some cases seem to be idiopathic. Symptoms are chronic cough and purulent sputum expectoration; some patients may also have fever and dyspnea. Diagnosis is based on history and imaging, usually involving high-resolution CT, though standard chest x-rays may be diagnostic. Treatment and prevention of acute exacerbations are with antibiotics, drainage of secretions, and management of complications, such as superinfection and hemoptysis. Treatment of underlying disorders is important whenever possible.

Etiology

Bronchiectasis is best considered the common end-point of various disorders that cause chronic airway inflammation. Bronchiectasis may affect many areas of the lung (diffuse bronchiectasis), or it may appear in only one or two areas (focal bronchiectasis).

Diffuse bronchiectasis develops most often in patients with genetic, immunologic, or anatomic defects that affect the airways. In developed countries, many cases appear initially to be idiopathic, probably partly because onset is so slow that the triggering problem cannot be identified by the time bronchiectasis is recognized. With newer, improved genetic and immunologic testing, an increasing number of reports describe finding an etiology in these idiopathic cases after careful, systematic evaluation.

Cystic fibrosis (CF) is the most common identified cause, and previously undiagnosed CF may account for up to 20% of idiopathic cases. Even heterozygous patients, who typically have no clinical manifestations of CF, may have an increased risk of bronchiectasis.

Immunodeficiencies such as common variable immunodeficiency (CVID) may also lead to diffuse disease, as may rare abnormalities in airway structure. Undernutrition and HIV infection also appear to increase risk.

Congenital defects in mucociliary clearance such as primary ciliary dyskinesia (PCD) syndromes may also be a cause, possibly also explaining some idiopathic cases.

Diffuse bronchiectasis sometimes complicates common autoimmune disorders, such as RA or Sjögren syndrome.

Allergic bronchopulmonary aspergillosis, a hypersensitivity reaction to *Aspergillus* spp. that occurs most commonly in people with asthma, but sometimes in patients with CF, can cause or contribute to bronchiectasis.

In developing countries, most cases are probably caused by TB, particularly in patients with impaired immune function due to undernutrition and HIV infection.

Focal bronchiectasis typically develops as a result of untreated pneumonia or obstruction (eg, due to foreign bodies, tumors, postsurgical changes, lymphadenopathy). Mycobacteria (tuberculous or nontuberculous) can both cause focal bronchiectasis and colonize the lungs of patients with bronchiectasis due to other disorders.

Pathophysiology

The pathophysiology of bronchiectasis is not fully understood, likely in part because it is the common end-point of a heterogenous group of disorders predisposing to chronic airway inflammation.

Diffuse bronchiectasis appears to start when a causative disorder triggers inflammation of small and medium-sized airways, releasing inflammatory mediators from intraluminal neutrophils. The inflammatory mediators destroy elastin, cartilage, and muscle in larger airways, resulting in irreversible bronchodilation. Simultaneously, in the inflamed small and medium-sized airways, macrophages and lymphocytes form infiltrates that thicken mucosal walls. This thickening causes the airway obstruction frequently noted during pulmonary function testing. With disease progression, inflammation spreads beyond the airways, causing fibrosis of the surrounding lung parenchyma. What inflames the small airways depends on the etiology of bronchiectasis. Common contributors include impaired airway clearance (due to production of thick, viscous mucus in CF, lack of ciliary motility in PCD, or damage to the cilia and/or airways secondary to infection or

injury) and impaired host defenses; these factors predispose patients to chronic infection and inflammation. In the case of immune deficiency (particularly CVID), autoimmune inflammation may also contribute.

Focal bronchiectasis usually occurs when a large airway becomes obstructed. The resulting inability to clear secretions leads to a cycle of infection, inflammation, and airway wall damage. The right middle lobe is involved most often because its bronchus is small and angulated and has lymph nodes in close proximity. Lymphadenopathy due to nontuberculous mycobacterial infection sometimes causes bronchial obstruction and focal bronchiectasis.

As ongoing inflammation changes airway anatomy, pathogenic bacteria (sometimes including mycobacteria), colonize the airways. Common organisms include *Haemophilus influenza* (35%), *Pseudomonas aeruginosa* (31%),*Moraxella catarrhalis* (20%), *Staphylococcus aureus* (14%), and *Streptococcus pneumonia* (13%). *S. Aureus* colonization is strongly associated with CF; a culture finding of *S. Aureus* should raise concern for undiagnosed CF. Also, colonization with *P. Aeruginosa* tends to indicate severe disease and portends a rapid decline in lung function. Colonization by multiple organisms is common, and antibiotic resistance is a concern in patients who require frequent courses of antibiotics for treatment of exacerbations.

Complications

As the disease progresses, chronic inflammation and hypoxemia cause neovascularization of the bronchial (not the pulmonary) arteries. Bronchial artery walls rupture easily, leading to massive hemoptysis. Other vascular complications include pulmonary hypertension due to vasoconstriction, arteritis, and sometimes shunt from bronchial to pulmonary vessels. Colonization with multidrug-resistant organisms can lead to chronic, low grade airway inflammation. This inflammation can progress to recurrent exacerbations and worsen airflow limitation on pulmonary function tests.

Symptoms and Signs

Symptoms characteristically begin insidiously and gradually worsen over years, accompanied by episodes of acute exacerbation.

The most common presenting symptom is chronic cough that produces thick, tenacious, often purulent sputum. Dyspnea and wheezing are common, and pleuritic chest pain can develop. In advanced cases, hypoxemia and right-sided heart failure due to pulmonary hypertension may increase dyspnea. Hemoptysis, which can be massive, occurs due to airway neovascularization.

Acute exacerbations are common and frequently result from new or worsened infection. Exacerbations are marked by a worsening cough and increases in dyspnea and the volume and purulence of sputum. Low-grade fever and constitutional symptoms (eg, fatigue, malaise) may also be present.

Halitosis and abnormal breath sounds, including crackles, rhonchi, and wheezing, are typical physical examination findings. Digital clubbing may be present. In advanced cases, signs of hypoxemia, pulmonary hypertension (eg, dyspnea, dizziness), and right-sided heart failure are common. Chronic rhinosinusitis and nasal polyps may be present, particularly in patients with CF or PCD. Lean body mass commonly decreases, possibly due to inflammation and cytokine excess and, in patients with CF, malabsorption.

Diagnosis

- History and physical examination
- Chest x-ray
- High-resolution chest CT
- Pulmonary function tests for baseline evaluation and monitoring disease progression
- Specific tests for suspected causes

Diagnosis is based on history, physical examination, and radiologic testing, beginning with a chest x-ray. Chronic bronchitis may mimic bronchiectasis clinically, but bronchiectasis is distinguished by increased purulence and volume of daily sputum and by dilated airways shown on imaging studies.

Imaging

Chest x-ray is usually abnormal and may be diagnostic. X-ray findings suggestive of bronchiectasis involve thickening of the airway walls and/or airway dilation; typical findings include ill-defined linear perihilar densities with indistinctness of the central pulmonary arteries, indistinct rings due to thickened airways seen in cross section (parallel to the x-ray beam), and “tram lines” (or tram-track sign) caused by thickened, dilated airways perpendicular to the x-ray beam. Dilated airways filled with mucous plugs can also cause scattered elongated, tubular opacities. Radiographic patterns may differ depending on the underlying disease; bronchiectasis due to CF develops predominantly in the upper lobes, whereas bronchiectasis due to an endobronchial obstruction causes more focal x-ray abnormalities.

High-resolution CT is the test of choice for defining the extent of bronchiectasis and is nearly 100% sensitive and specific. Typical CT findings include airway dilation (in which the inner lumen of two or more airways exceed the diameter of the adjacent artery) and the signet ring sign (in which a thickened, dilated airway appears adjacent to a smaller artery in transaxial view). Lack of normal bronchial tapering can result in visible medium-sized bronchi extending almost to the pleura. "Tram lines" are easily visible on CT. As airway damage increases over time, bronchiectasis changes progress from cylindrical to varicose and then cystic findings on imaging. Atelectasis, consolidation, mucus plugs, and decreased vascularity are nonspecific findings. In traction bronchiectasis, pulmonary fibrosis pulls or distorts airways in ways that simulate bronchiectasis on imaging.

Pulmonary function tests

Pulmonary function tests can be helpful for documenting baseline function and for monitoring disease progression. Bronchiectasis causes airflow limitation (reduced forced expiratory volume in 1 sec [FEV_1], forced vital capacity [FVC], and FEV_1/FVC); the FEV_1 may improve in response to β-agonist bronchodilators. Lung volume measurements may be increased or decreased, and diffusing capacity for carbon monoxide (DL_{CO}) may be decreased.

Diagnosis of cause

During an exacerbation-free period, all patients should have expectorated or induced sputum cultured to determine the predominant colonizing bacteria and their sensitivities. This information helps with antibiotic selection during exacerbations. A CBC and differential can help determine the severity of disease activity and identify eosinophilia, which may suggest complicating diagnoses. Staining and cultures for bacterial, mycobacterial (*Mycobacterium avium* complex and *M. tuberculosis*), and fungal *(Aspergillus* spp) organisms may also help identify the cause of chronic airway inflammation. Clinically significant nontuberculous mycobacterial infection is diagnosed by finding high colony counts of these mycobacteria in cultures from serial sputum samples or from bronchoalveolar lavage fluid in patients who have granulomas on biopsy or concurrent radiologic evidence of disease.

When the cause of bronchiectasis is unclear, additional testing based on the history and imaging findings may be done. Tests may include the following:

- Serum immunoglobulins (IgG IgA, IgM) and serum electrophoresis to diagnose CVID
- Targeted assessment of baseline and specific antibody responses to peptide and polysaccharide antigens (ie, tetanus, capsular polysaccharide of *S. Pneumonia* and *H. Influenza* type b) done to assess immune responsiveness
- Two sweat chloride tests and *CFTR* gene mutation analysis to diagnose CF (including in adults > 40 yr without an identifiable cause of bronchiectasis, especially if they have upper lobe involvement, malabsorption, or male infertility)
- Rheumatoid factor, ANA, and antineutrophil cytoplasmic antibody testing if an autoimmune condition is being considered
- Serum IgE and *Aspergillus* precipitins if patients have eosinophilia, to rule out allergic bronchopulmonary aspergillosis
- α_1-Antitrypsin level to evaluate for α_1-antitrypsin deficiency if high resolution CT shows lower lobe emphysema

PCD should be considered if adults with bronchiectasis also have chronic sinus disease or otitis media, particularly if problems have persisted since childhood. Bronchiectasis in such patients may have right middle lobe and lingular predominance, and infertility or dextrocardia may be present. Diagnosis requires examination of a nasal or bronchial epithelial sample for abnormal ciliary structure using transmission electron microscopy. The diagnosis of PCD should typically be done in specialized centers because evaluation can be challenging. Nonspecific structural defects can be present in up to 10% of cilia in healthy people and in patients with pulmonary disease, and infection can cause transient dyskinesia. Ciliary ultrastructure may also be normal in some patients with PCD syndromes, requiring further testing to identify abnormal ciliary function.

Bronchoscopy is indicated when an anatomic or obstructive lesion is suspected.

Evaluation of exacerbations

The degree of testing depends on the severity of the clinical presentation. For patients with mild to moderate exacerbations, repeat sputum cultures to confirm the causative organism and sensitivity patterns may be sufficient. These help narrow antibiotic coverage and exclude opportunistic pathogens. For more severely ill patients,a CBC, chest x-ray, and possibly other tests may be warranted to exclude common complications of serious pulmonary infection, such as lung abscess and empyema.

Prognosis

Prognosis varies widely. Mean yearly decrease in FEV_1 is about 50 to 55 mL (normal decrease in healthy people is about 20 to 30 mL). Patients with CF have the poorest prognosis, with a median survival of 36 yr, and most patients continue to have intermittent exacerbations.

Treatment

- Prevention of exacerbations with regular vaccinations and sometimes suppressive antibiotics
- Measures to help clear airway secretions
- Bronchodilators and often inhaled corticosteroids if reversible airway obstruction is present
- Antibiotics and bronchodilators for acute exacerbations
- Sometimes surgical resection for localized disease with intractable symptoms or bleeding

The key treatment goals are to control symptoms and improve quality of life, reduce the frequency of exacerbations, and preserve lung function.

As for all patients with chronic pulmonary disease, smoking cessation and annual influenza vaccination and pneumococcal polysaccharide vaccination are recommended. Revaccination is recommended 5 yr later in patients who are < 65 at the time of their initial pneumococcal vaccination and for patients who are asplenic or immunosuppressed.

Airway clearance techniques are used to reduce chronic cough in patients with significant sputum production and mucus plugging and to reduce symptoms during exacerbations. Such techniques include postural drainage and chest percussion, positive expiratory pressure devices, intrapulmonary percussive ventilators, pneumatic vests, and autogenic drainage (a breathing technique thought to help move secretions from peripheral to central airways). Patients should be taught these techniques by a respiratory therapist and should use whichever one is most effective and sustainable for them; no evidence favors one particular technique.

For patients with reversible airway obstruction, bronchodilator therapy (eg, with some combination of a long-acting β-adrenergic agonist, tiotropium, and a short-acting β-adrenergic drug as indicated by symptoms, as used in patients with COPD) can help improve function and quality of life. Inhaled corticosteroids may also be used in patients with frequent exacerbations or marked variability in lung function measurements. Pulmonary rehabilitation can be helpful.

In patients with CF, a variety of nebulized treatments, including a mucolytic (rhDNase) and hypertonic (7%) saline, can help reduce sputum viscosity and enhance airway clearance. In patients without CF, evidence of benefit with these agents is inconclusive, so only humidification and saline are recommended as inhaled treatments. Inhaled terbutaline, and mucolytics such as carbocysteine and bromhexine have mechanisms that might be expected to accelerate tracheobronchial clearance. However, most of these agents have had mixed results in limited trials in patients with and without CF.

There is no consensus on the best use of antibiotics to prevent or limit the frequency of acute exacerbations. Use of suppressive antibiotics regularly or on a rotating schedule reduces symptoms and exacerbations but may increase the risk that future infections will involve resistant organisms. Current guidelines suggest using antibiotics in patients with ≥ 3 exacerbations per year and possibly also in those with fewer exacerbations who have culture-proven *P. Aeruginosa* colonization. Chronic therapy with azithromycin 500 mg po 3 times/wk reduces acute exacerbations in patients with or without CF. Macrolides are thought to be beneficial mainly due to their anti-inflammatory or immunomodulatory effects. Patients with *P. Aeruginosa* may benefit from inhaled tobramycin, 300 mg bid given for a month every other month.

Additional treatment depends on the cause.

Allergic bronchopulmonary aspergillosis is treated with corticosteroids and sometimes azole antifungals. Patients with immunoglobulin or α_1-antitrypsin deficiencies should receive replacement therapy.

Acute exacerbations

Acute exacerbations are treated with antibiotics, inhaled bronchodilators (particularly if patients are wheezing), and increased attempts at mucus clearance, using mechanical techniques, humidification, and nebulized saline (and mucolytics for patients with CF). Inhaled or oral corticosteroids are given to treat airway inflammation. Antibiotic choice depends on previous culture results and whether or not patients have CF.

Initial antibiotics for patients without CF and with no prior culture results should be effective against *H. influenzae*, *M. catarrhalis*, *S. aureus*, and *S. pneumoniae*. Examples include amoxicillin/clavulanate, azithromycin, clarithromycin, and trimethoprim/sulfamethoxazole. Antibiotics should be adjusted based on culture results and given for a typical duration of 14 days. Patients with known *P. Aeruginosa* colonization or more severe exacerbations should receive antibiotics effective against this organism (eg, ciprofloxacin 500 mg po bid, levofloxacin 500 mg po once/day for 7 to 14 days) until repeat culture results are available.

Initial antibiotic selection for patients with CF is guided by previous sputum culture results (done routinely in all patients with CF). During childhood, common infecting organisms are *S. Aureus* and *H. influenzae*, and quinolone antibiotics such as ciprofloxacin and levofloxacin may be used. In the later stages of CF, infections involve highly resistant strains of certain gram-negative organisms including *P. aeruginosa*, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia*. In patients with infections caused by these organisms, treatment is with multiple antibiotics (eg, tobramycin, aztreonam, ticarcillin/clavulanate, ceftazidime, cefepime). IV administration is frequently required.

Complications

Significant hemoptysis is usually treated with bronchial artery embolization, but surgical resection may be considered if embolization is ineffective and pulmonary function is adequate.

Superinfection with mycobacterial organisms such as *M. Avium* complex almost always requires multiple drug regimens that include clarithromycin 500 mg po bid or azithromycin 250 mg po once/day; rifampin 600 mg po once/day or rifabutin 300 mg po once/day; and ethambutol 25 mg/kg po once/day for 2 mo followed by 15 mg/kg po once/day. Drug therapy is modified based on culture and sensitivity results. All drugs should be taken until sputum cultures have been negative for 12 mo.

Surgical resection is rarely needed but may be considered when bronchiectasis is localized, medical therapy has been optimized, and the symptoms are intolerable. In certain patients with diffuse bronchiectasis, lung transplantation is also an option. Five-year survival rates as high as 65 to 75% have been reported when a heart-lung or double lung transplantation is done. Pulmonary function usually improves within 6 mo, and improvement may be sustained for at least 5 yr.

Key Points

- In bronchiectasis, chronic inflammation from various causes destroys elastin, cartilage, and muscle in larger airways, resulting in irreversible bronchodilation; dilated airways are chronically colonized by infectious organisms.

- Patients have chronic productive cough with intermittent acute exacerbations, usually 2 to 3 times/yr.
- Diagnosis is with imaging, usually CT; cultures should be done to identify colonizing organism(s).
- Prevent exacerbations using appropriate immunizations, airway clearance measures, and sometimes macrolide antibiotics
- Treat exacerbations with antibiotics, bronchodilators, more frequent airway clearance measures, and corticosteroids.

Lung abscess

is a necrotizing lung infection characterized by a pus-filled cavitary lesion. It is most commonly caused by aspiration of oral secretions by patients who have impaired consciousness. Symptoms are persistent cough, fever, sweats, and weight loss. Diagnosis is based primarily on chest x-ray. Treatment usually is with clindamycin or combination β-lactam/β-lactamase inhibitors.

Etiology

- Aspiration of oral secretions (most common)
- Endobronchial obstruction
- Hematogenous seeding of the lungs (less common)

Most lung abscesses develop after aspiration of oral secretions by patients with gingivitis or poor oral hygiene. Typically, patients have altered consciousness as a result of alcohol intoxication, illicit drugs, anesthesia, sedatives, or opioids. Older patients and those unable to handle their oral secretions, often because of neurologic disease, are also at risk. Lung abscesses can also develop secondary to endobronchial obstruction (eg, due to bronchial carcinoma) or to immunosuppression (eg, due to HIV/AIDS or after transplantation and use of immunosuppressive drugs).

A less common cause of lung abscess is necrotizing pneumonia that may develop from hematogenous seeding of the lungs due to suppurative thromboembolism (eg, septic embolism due to IV drug use) or right-sided endocarditis. In contrast to aspiration and obstruction, these conditions typically cause multiple rather than isolated lung abscesses.

Pathogens

The most common pathogens of lung abscesses due to aspiration are anaerobic bacteria, but about half of all cases involve both anaerobic and aerobic organisms (see Infectious Causes of Cavitary Lung Lesions). The most common anaerobic pathogens are *Peptostreptococcus*, *Fusobacterium*, *Prevotella*, and *Bacteroides*. The most common aerobic pathogens are streptococci and staphylococci—sometimes methicillin-resistant *Staphylococcus aureus* (MRSA). Occasionally, cases are due to gram-negative bacteria, especially *Klebsiella*. Immunocompromised patients with lung abscess are most commonly infected with *Pseudomonas aeruginosa*and other gram-negative bacilli but also may have infection with *Nocardia*, *Mycobacteria* sp, or fungi. Rare cases of pulmonary gangrene or fulminant pneumonia with sepsis have been reported with pathogens such as MRSA, *Pneumococcus*, and *Klebsiella*. Some patients, especially those from developing countries, are at risk of abscess due to *Mycobacterium tuberculosis*, and rare cases are due to amebic infection (eg, with *Entamoeba histolytica*), paragonimiasis, or infection with *Burkholderia pseudomallei*.

Introduction of these pathogens into the lungs first causes inflammation, which, over a week or two, leads to tissue necrosis and then abscess formation. The abscess usually ruptures into a bronchus, and its contents are expectorated, leaving an air- and fluid-filled cavity. In about one third of cases, direct or indirect extension (via bronchopleural fistula) into the pleural cavity results in empyema.

Symptoms and Signs

Symptoms of abscess due to anaerobic bacteria or mixed anaerobic and aerobic bacteria are usually chronic (eg, occurring over weeks or months) and include productive cough, fever, night sweats, and weight loss. Patients may also present with hemoptysis and pleuritic chest pain. Sputum may be purulent or blood-streaked and classically smells or tastes foul.

Symptoms of abscess due to aerobic bacteria develop more acutely and resemble bacterial pneumonia. Abscesses due to organisms other than anaerobes (eg, *Mycobacteria*, *Nocardia*) lack putrid respiratory secretions and may be more likely to occur in nondependent lung regions.

Signs of lung abscess, when present, are nonspecific and resemble those of pneumonia: decreased breath sounds indicating consolidation or effusion, temperature ≥ 38 C, crackles over the affected area, egophony, and dullness to percussion in the presence of effusion. Patients typically have signs of periodontal disease and a history of a predisposing cause of aspiration, such as dysphagia or a condition causing impaired consciousness.

Diagnosis

- Chest x-ray
- Sometimes CT
- Sputum cultures (unless anaerobic infection is very likely), including for fungi and mycobacteria
- Bronchoscopy as needed to exclude cancer, detect unusual pathogens such as fungi or mycobacteria, and in immunocompromised patients
- Culture of any pleural fluid

Lung abscess is suspected based on history in a patient who is aspiration-prone due to altered consciousness or dysphagia and is confirmed by chest x-ray showing cavitation.

Cavitary pulmonary lesions are not always caused by infection. Noninfectious causes of cavitary pulmonary lesions include the following:

- Empyema or bulla with air-fluid level
- Cystic (saccular) bronchiectasis
- Lung cancer
- Lung infarction
- Nodular silicosis nodule with central necrosis
- Pulmonary embolism
- Pulmonary sequestration
- Sarcoidosis
- Granulomatosis with polyangiitis (Wegener granulomatosis)

In an anaerobic infection due to aspiration, chest x-ray classically shows consolidation with a single cavity containing an air-fluid level in portions of the lung that would be dependent when the patient is recumbent (eg, the posterior segments of the upper lobes or the superior or lateral basal segments of the lower lobes). This pattern helps distinguish anaerobic abscess from other causes of cavitary pulmonary disease, because diffuse or embolic pulmonary disease often causes multiple cavitations, and TB typically involves the apices.

CT is not routinely needed (eg, if cavitation is clear on chest x-ray in a patient who has risk factors for lung abscess). However, CT may be useful when cavitation is suggested but not clearly seen on the chest x-ray, when an underlying pulmonary mass obstructing the drainage of a lung segment is suspected, or when abscess needs to be differentiated from empyema or bulla with an air-fluid level.

Bronchial carcinoma can lead to obstruction that causes pneumonia and abscess formation. Bronchial carcinoma should be suspected in patients who do not respond to antimicrobial treatment or have atypical findings such as a cavitary lesion and no fever. Bronchoscopy is sometimes done to exclude cancer or the presence of a foreign body or to detect unusual pathogens, such as fungi or mycobacteria. Bronchoscopy is done if patients are immunocompromised.

Cultures

Anaerobic bacteria are rarely identifiable on culture because uncontaminated specimens are difficult to obtain and because most laboratories do not culture anaerobes well or often. If sputum is putrid, then anaerobic infection is assumed to be the cause. However, if empyema is present, pleural fluid provides a good source for anaerobic culture.

When clinical findings make anaerobic infection less likely, aerobic, fungal, or mycobacterial infection should be suspected, and attempts should be made to identify a pathogen. Cultures of sputum, bronchoscopic aspirates, or both are helpful.

Treatment

- IV antibiotics or, for less seriously affected patients, oral antibiotics
- Percutaneous or surgical drainage of any abscess that does not respond to antibiotics or of any empyema

Treatment is with antibiotics. Clindamycin 600 mg IV q 6 to 8 h is usually the drug of choice because it has excellent activity against streptococci and anaerobic organisms. The primary alternative is a combination β-lactam/β-lactamase inhibitor (eg, ampicillin/sulbactam 1 to 2 g IV q 6 h). Other alternatives include a carbapenem (eg, imipenem/cilastatin 500 mg IV q 6 h) or combination therapy with metronidazole 500 mg q 8 h plus penicillin 2 million units IV q 6 h. Less seriously ill patients may be given oral antibiotics such as clindamycin 300 mg po q 6 h or amoxicillin/clavulanate 875/125 mg po q 12 h. IV regimens can be converted to oral ones when the patient defervesces. For very serious infections involving MSRA, the best treatment is vancomycin or linezolid.

Optimal duration of treatment is unknown, but common practice is to treat until the chest x-ray shows complete resolution or a small, stable, residual scar, which generally takes 3 to 6 wk or longer. In general, the larger the abscess, the longer it will take for x-rays to show resolution.

Most authorities do not recommend chest physical therapy and postural drainage because of the potential for spillage of infection into other bronchi with extension of the infection or acute obstruction.

An accompanying empyema must be drained. Surgical removal or drainage of lung abscesses is necessary in the roughly 10% of patients in whom lesions do not respond to antibiotics, and those who develop pulmonary gangrene. Resistance to antibiotic treatment is most common with large cavities and with post-obstructive abscesses. If patients fail to defervesce or to improve clinically after 7 to 10 days, they should be evaluated for resistant or unusual pathogens, airway obstruction, and noninfectious causes of cavitation.

When surgery is necessary, lobectomy is the most common procedure; segmental resection may suffice for small lesions (<6 cm diameter cavity). Pneumonectomy may be necessary for multiple abscesses unresponsive to drug therapy or for pulmonary gangrene. In patients likely to have difficulty tolerating surgery, percutaneous drainage or, rarely, bronchoscopic placement of a pigtail catheter can help facilitate drainage.

Equipment: class room, Harvey cardiopulmonary patient simulator, 6-channel ECG machine CARDIOLINE 100 L and Cardioline 200 + II S, Electric pump (Aspirator) Medela Clario

Lesson time: 2 hours

Plan

I. Organization moments (Greeting, roll-call, theme announce, aim of lesson, applicants motivation to study the topic).

II. Control of basic knowledges (The task source for self-knowledge skills tests from «KROK2» - additional materials, cheking workbooks)

II.1 Requirements for theoretical readiness of applicants to perform practical classes.

Requirements to knowledges:

- Definition of infective destructive bronchopulmonary diseases
- Modern aspects of etiology and pathophysiology of infective destructive bronchopulmonary diseases
- Classification of infective destructive bronchopulmonary diseases
- Clinical manifestation of infective destructive bronchopulmonary diseases
- Laboratory and instrumental investigation of infective destructive bronchopulmonary diseases
- Carry out differential diagnosis of infective destructive bronchopulmonary diseases

- Complications of infective destructive bronchopulmonary diseases
- Treatment, rehabilitation of patients with infective destructive bronchopulmonary diseases
- Prognosis and disability of patients with infective destructive bronchopulmonary diseases

List of didactic units

- To get a detailed anamnesis
- To do physical examination of patient, to diagnose and to estimate changes in condition
- To make a plan of additional investigation and estimate it
- Justify and make a preliminary and clinical diagnoses of infective destructive bronchopulmonary diseases based on severity of airflow limitation, complex evaluation of infective destructive bronchopulmonary diseases
- Estimation of exacerbation of infective destructive bronchopulmonary diseases
- Estimation of clinical examination, CBC, blood tests, sputum tests, chest X-Ray, CT scan and etc.

II.2 Questions (MSQ, clinical cases) for basic knowledge examination of topic

1. A 35 y.o. woman was admitted to thoracic surgery department with fever up to 40^0C, onset of pain in the side caused by deep breathing, cough with considerable quantity of purulent sputum and blood with bad smell. What is the most likely diagnosis?
A. Abscess of the lung. +
B. Complication of liver echinococcosis.
C. Bronchiectatic disease.
D. Actinomycosis of lungs.
E. Pulmonary tuberculosis.
2. A patient with nosocomial pneumonia presents signs of collapse. Which of the following pneumonia complications is most likely to be accompanied by collapse?
A. Septic shock.+
B. Exudative pleuritis.
C. Bronchial obstruction.
D. Toxic hepatitis.
E. Emphysema.
3. A 30 y.o. man presents with a history of recurrent pneumonias and a chronic cough production of foul smelling, purulent sputum, occasionally glood tinged, which is worse in the morning and on lying down. On physical examination, the patient appears chronically ill with clubbing of fingers, inspiratory rales at the base of lungs posteriorly. Most likely diagnosis:
A. Bronchoectasis. +
B. Chronic bronchitis.
C. Disseminated pulmonary tuberculosis.
D. Pulmonary neoplasm.
E. Chronic obstructive emphysema.
4. A patient complains of a tormental (agonizing) cough with expectoration of up to 600 ml/daily purulent chocolatecolor sputum with a decay smell. Onset of illness was abrupt, 39ºC fever of irregular type. There is the area of darkening with a cavity in a center on chest X-ray, with irregular contours and level of liquid. What disease is the question?
B. Gangrene of lung. +
C. Tuberculosis.
D. Bronchiectatic disease.
E. Pneumonia complicated by an abscess.
E. Lobar pneumonia.
5. A 55 y.o. male patient complains of weakness during 2 months, pain in the right side of the thorax, cough, blood-streaked sputum. On X-ray: intensive triangle shadow in the area of lower lobe that is connected to mediastinum. What is the most likely disorder in the lungs?

A. Central cancer of lungs.
B. Tuberculosis of lungs.
C. Bronchiectasia.
D. Pulmonary infarction. +
E. Pleuropneumonia.
6. A patient 17 y.old, is disturbed by the cough, more intensive in the morning with a mucoid-purulent sputum to 100 ml a day, often with admixture of blood. During the period of exacerbation the quantity of sputum increases to 300-400 ml. Has been ill for 10 years. Fingers in the shape of drum sticks, shortening of a percussion sound in inferolateral part of a right lung, here there's a focus of fine moist rales. Your preliminary diagnosis:
A. Diffuse pulmonary fibrosis.
B. Pulmonary abscess.
C. Chronic obstructive bronchitis.
D. Pulmonary tuberculosis.
E. Multiple bronchiectasis.+
7. A 20 y.o. female patient is suffering from chronic bronchitis. Recently there has been production about 0,5 L of purulent sputum with maximum discharge in the morning. Fingers are like "drum sticks", there are "watching glass" nails. What is the most probable diagnosis?
A.Bronchiectasia +
B.Pneumonia
C.Chronic bronchitis
D.Gangrene of lungs
E.Tuberculosis
8. Indications for surgical treatment of IDD of broncho-pulmonary system does not include:
A. pneumoempyema
B. chronicity abscess
C. recurrent bleeding
D. empyema
E. mediastinal emphysema +

III. Proffesional skills formation (skills of patient`s management, treatment)
Professional algorithms: work with a patient (according to patients-applicants conversation algorithm).

During examination students must use next algorithm:

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Collecting data on patient complains, medical history, life history
5. Interpretation of clinical, laboratory and instrumental studies
6. Explanation for patient of next acting (hospitalization, workup)
7. End of conversation

Physical examination of patient with internal diseases

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Explanation of investigations are needed, taking agreement
5. Telling about possible negative feelings during investigation
6. Preparing to examination (clean warm hands, accurate nails, warm phonendoscope, screen if needed)
7. Examination (demonstration of clinical skills)
8. Interpretation of clinical, laboratory and instrumental studies

9. End of conversation

Telling to patient with internal diseases investigation results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of investigation results
5. Conversation with patient (comparing new and previous examination results, check if explanation is clear)
6. End of conversation

Planning and prognosing treatment results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of treatment
5. Conversation with patient (explanation of features taking pills, duration of taking drugs, possible side effects)
6. Check if explanation is clear
7. End of conversation

Telling treatment prognosis

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of expected treatment results
5. Conversation with patient (explanation of importance of life-long treatment, taking medications according to list, check if explanation is clear)
6. End of conversation

Task 1

1. Collecting complains, anamnesis, examination of patients with bronchial asthma
2. Identify clinical and instrumental symptoms
3. Make a syndrome based on symptoms
4. Identify the leading clinical syndrome
5. Assign laboratory and instrumental examination (CBC, urine analysis, blood tests, sputum tests, spirometry, bronchodilatation test, chest X-Ray, ECG, EchoCG and others)
6. Carry out differential diagnosis with pneumonia, lung cancer
7. Make a clinical diagnosis
8. Determine a degree of disability

Task 2

Prescribing different variants of treatment according to guidelines

Task 3

Work in Internet, work with thematic literature in department library room.
Student must fill patient examination protocol (example is added).

Control materials for final part of the lesson:

The cases for self-control with standard answers.

1. A 55 y.o. male patient complains of weakness during 2 months, pain in the right side of the thorax, cough, blood-streaked sputum. On X-ray: intensive triangle shadow in the area of lower lobe that is connected to mediastinum. What is the most likely disorder in the lungs?

A Bronchoectasia

B Central cancer of lungs
C Tuberculosis of lungs
D Pulmonary infarction
E Pleuropneumonia

2. A patient complains about strong dyspnea that is getting worse during physical activity. Presentations appeared suddenly 2 hours ago at work: acute chest pain on the left, cough. The pain was abating, but dyspnea, dizziness, pallor, cold sweat and cyanosis were progressing. Vesicular respiration is absent, X-ray picture shows a shadow on the left. What pathology might be suspected?

A Spontaneous left-sided pneumothorax
B Pulmonary infarction
C Pleuritis
D Left-sided pneumonia
E Pulmonary abscess

3. A 32 y.o. patient who has been staying in a hospital on account of acute abscess of his right lung suddenly felt pain after coughing in the right half of thorax, he got heavy breathing, cyanosis. What complication is the most probable?

A Esophagus perforation
B Infarction-pneumonia
C Myocardial infarction
D Pyopneumothorax
E Exudative pleurisy

4. A 35 y.o. patient was admitted to the local hospital a week after a road accident with clinical picture of clotted hemothorax. What is the most appropriate treatment tactic for prevention of acute pleural empyema?

A Active drainage of pleural cavity
B Treatment by pleural punctions
C Complex conservative therapy
D Passive drainage of pleural cavity
E Surgical removal of clotted hemothorax

5. After 4 days after undergoing cold patient hospitalized with complaints of mild productive cough with mucous expectoration. On the second day of hospitalization once expectorated about 250 ml purulent sputum streaked with blood. RR -28-30 / min. PS – 96 bpm, BP -110/70 mmHg Vesicular breathing over the left lung, on the right – weakening of vesicular breathing, variegated crackles over the lower part and amphoric breathing near scapula's angle. What is the preliminary diagnosis?

A. Acute lung abscess
B. Empyema
C. Pneumoempyema
D. Acute focal pneumonia
E. Pleural effusion

6. Patient 29 y.o., for 2 months complains of pain in the left half of the chest, cough, shortness of breath, fever up to 39.5°C. Objectively: the left half of the chest delayed in the act of breathing, the weakening of vesicular breathing and shortening of percussion sound on the left. X-ray determined the round shadow in the lower lobe of the left lung. What is the preliminary diagnosis?

A. Purulent pleurisy
B. Plevral empyema
C. Lung abscess
D. Chronic pneumonia
E. Lung cancer

7. The patient 52 years complains of pain in the right half of chest, shortness of breath, cough with a lot quantity of foamy sputum in the form of "meat slops", with an unpleasant smell. OBJECTIVE:

The state – severe gravity, cyanosis, RR-31 / min, dullness of percussion sound over the right lung, auscultation - mixed moist rales. What is the most probable diagnosis?
A. Bronchiectasis
B. Lung abscess
C. Chronic pneumonia
D. Pleural empyema
E. Lung gangrene
8. Patient 62 years, current smoker, often suffers from "pneumonia". On chest X-ray in the right lung found triangular shape shadow with the apex directed to the root of the lung and shift of heart and mediastinum toward to the lesions. What is the most likely diagnosis?
A. Lung cancer
B. Lung cyst
C. Lung abscess
D. Lung atelectasis
E. Lung infarction
9. The patient 32 y.o. is acutely ill after hypothermia. T 40ºC, cough with 200 ml sputum per day. Sputum purulent, with an unpleasant odor. Right lung - over the lower lobe moist variegated rales. In the blood: WBC – $18x10^9$ / l, ESR - 45 mm / h. X-ray: in the right lower lobe defined thick-walled cavity 6 cm in diameter with high horizontal level. What disease is most likely?
A Lung cyst
B Lung tuberculosis
C Lung abscess
D Lung cancer
E Bronchoectasis
10. A patient 17 y.o., is disturbed by the cough, more intensive in the morning with a mucoid-purulent sputum to 100 ml a day, often with admixture of blood. During the period of exacerbation the quantity of sputum increases to 300-400 ml. Has been ill for 10 years. Fingers in the shape of drum sticks, shortening of a percussion sound in inferolateral part of a right lung, here there's a focus of fine moist rales. Your preliminary diagnosis:
A. Diffuse pulmonary fibrosis.
B. Pulmonary abscess.
C. Chronic obstructive bronchitis.
D. Pulmonary tuberculosis.
E. Multiple bronchiectasis.
Standard answers: 1-B, 2-A, 3-D, 4-A, 5-A, 6-C, 7-E, 8-D, 9-C, 10-E.

IV. Making conclusions, telling final marks, tasks for the next lesson

Literature list:
- Basic literature source:
1. ERS Guidelines on the Management of adult non-cystic fibrosis bronchiectasis, 2017
2. Harrison's Manual in Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 1245 p.
3. Harrison's Principles of Internal Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 3528 p.
- Additional literature source:
1. Wei-jie Guan, Rong-chang Chen, Nan-shan Zhong/European Respiratory Journal Feb 2016, 47 (2) 382-384;

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European male of 40 years old.

COMPLAINTS: fever, shaking, chills and malaise after supercooling

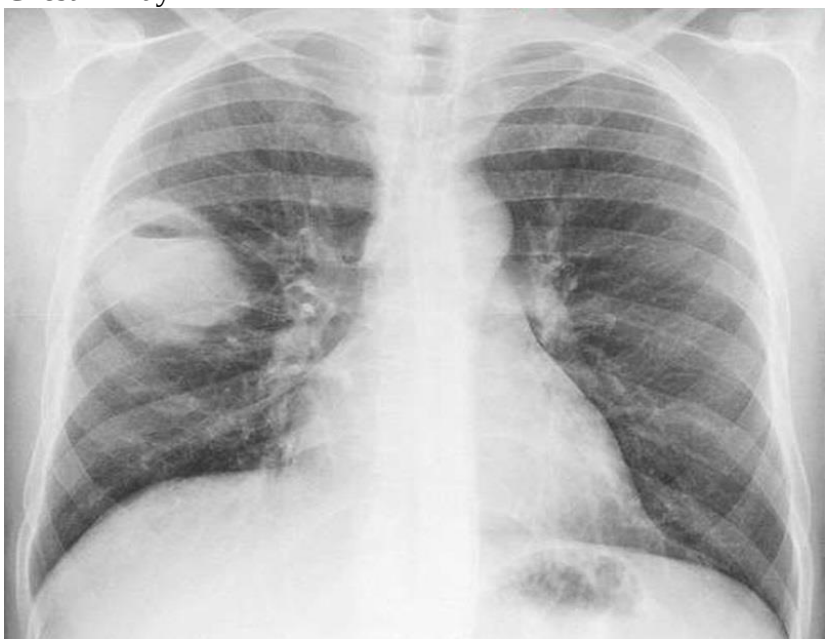
HISTORY: Mr. B. is a 40 year old man who developed a harsh, non-productive cough four days prior to being seen by a physician. Today patient mentioned that cough becomes productive, with yellow sputum. He developed a fever, shaking, chills and malaise along with the cough.

PHYSICAL EXAMINATION: Vital signs are as follows: blood pressure 120/85, apical heart rate 100/minute and regular, respiratory rate 22 per minute and somewhat labored, temperature 40˚C. Both lungs are resonant by percussion with one exception: dull sound in the mid-lobe of the right lung. Auscultation: reveals bilateral diminished vesicular breath sounds, above mid-lobe of the right lung absence of breath sounds. The remainder of the lung fields is clear. Percussion and auscultation of the heart reveals no significant abnormality. Abdomen is not painful. No peripheral edema.

Examination plan:

1. Cell blood count,
2. blood biochemistry: creatinine, urea
3. coagulation test,
4. liver function tests
5. Chest X-Ray
6. ECG
7. Sputum test

Chest X-Ray



CBC: WBC-17 G/l, left side-shift formula, ESR 67%.

Sputum test: WBC in all field of vision

Another blood tests, ECG without pathological signs

Diagnosis:

Mid-lobe right lung abscess

Treatment plan:

1. Cefoperazone, sulbactam 1.0/1,0 g i.v. 2 times per day, 10 days
2. Ciprofloxacine 500 mg once a day, 10 days
3. Ambroxol 15 mg i.v. 2 times per day
4. Paracetamol 500 mg 2 times per day
5. Sol. «Reosorbilact» 200 ml i.v. once a day

Practical lesson № 19

Theme: Pulmonary insufficiency

Object: To teach applicants to master the method of examination of patients with respiratory diseases with the selection of the main pulmonological syndromes. To study probable etiological factors, pathogenesis of pulmonary insufficiency, their main clinical forms, variants of disease course, differential diagnosis, treatment tactics, determination of prognosis and efficiency of patients.

Basic concepts:

№	Term	Definition
1	Hypoxemia	abnormally low level of oxygen in the blood (PaO2 is lower than 60 mmHg,
2	Hypercapnia	elevation in the partial pressure of carbon dioxide (PaCO2) above 45 mm Hg on Arterial Blood Gas readings
3	ABG	test measures the acidity (pH) and the levels of oxygen and carbon dioxide in the blood from an artery. This test is used to find out how well lungs are able to move oxygen into the blood and remove carbon dioxide from the blood.
4	Cheyne-Stokes breathing	The pattern involves a period of fast, shallow breathing followed by slow, heavier breathing and moments without any breath at all, called apneas

Content of practical lesson

Pulmonary insufficiency – it is a condition in which the lung cannot fulfill its primary function of maintaining adequate gas exchange leading to PaO_2 less than 60mmHg and/or $PaCO_2$ more than 50 mmHg .

Etiology

- Airway obstruction: Airway inflammation, tumor, foreign bodies, fibrosis scar COPD and asthma
- Alveolar or interstitial lung diseases: pneumonia, emphysema, pulmonary tuberculosis, diffuse interstitial pulmonary fibrosis, pulmonary edema
- Pulmonary vascular diseases: Pulmonary embolism, pulmonary vasculitis
- Chest wall or pleural diseases: Flail chest caused by trauma, pneumothorax, severe spinal deformity, massive pleural effusion
- Neuromuscular diseases: Cerebrovascular diseases, craniocerebral trauma, cerebritis and sedative-hypnotic, poliomyelitis, polyneuritis, myasthenia gravis

Pathogenesis

Hypoxemia

- Alveolar ventilation ↓
- FiO_2↓
- Diffusion abnormality
- V/Q mismatch : V/Q>0.8 or V>Q - dead space effect
  A-V shunt (V/Q < 0.8 or Q>V)

Hypercapnia(CO2 retention)

- CO_2 production↑ (fever, infection, sepsis, epilepsy)

Alveolar ventilation ↓(neuromuscular diseases or fatigue of respiratory muscles • obstructive ventilation disorder)

Classification

According to pathophysiology and arterial blood gas analysis:

Type I: A failure of gas exchange

Hypoxemia, PaO2 < 60 mmHg
Type II: A failure of ventilation
PaO_2 < 60 mmHg, $PaCO_2$ > 50 mmHg
PaO_2 > 60 mmHg, $PaCO_2$ >50 mmHg
Iatrogenic

According to the involved site

Central respiratory failure

- Change of respiratory rhythm and frequency

Peripheral respiratory failure

- Dyspnea

According to onset of respiratory failure

- Acute, develops in seconds or hours
- Chronic, develops in days or longer, elevated HCO3-
- Acute onset of Chronic respiratory failure
- Have no definitive borderline

According to mechanisms

Pump failure is caused by dysfunction of respiratory pump; characterized by

- Low respiratory drive due to central or peripheral nervous system diseases, neuromuscular junction problem or fatigue of respiratory muscles→hypoventilation
- manifested as type Ⅱ respiratory failure

Lung failure is caused by disorder of lung parenchyma, pulmonary vascular or airway obstruction

-Airway obstruction → hypoventilation, manifested as type Ⅱ respiratory failure

- Disorder of lung parenchyma → dysfunction of oxygenation, manifested as hypoxemia
- Disorder of pulmonary vascular system → ventilation/perfusion mismatch, manifested as hypoxemia

Classification of PI (LF)according to functional parameters
Restrictive: TLC < 80%, FEV1/VC >85%
Obstructive: FEV1/VC)< 70%
Mixed
Classification of PI according to degree of severity

Degree	PaO2, mmHg	SaO2, %
Normal	≥80	≥95
I	60–79	90–94
II	40–59	75–89
III	<40	<75

Influence of hypoxemia

Central nervous system

Oxygen consumption of brain--3 ml/100g·min
If jugular vein PaO2 <20mmHg: unconsciousness, coma
PaO2 <20mmHg: irreversible damage to nerve cells in several minutes (4~5min)
Mild hypoxemia: impaired concentration, disorientation, hypomnesia
Severe hypoxemia: dysphoria, unconsciousness, coma

Cardiovascular system

Myocardium oxygen consumption: 10 ml/100g/min

Early stage of acute hypoxia–stimulation of sympathetic nerve→HR↑、BP↑、CO ↑

Chronic hypoxia → small pulmonary arteries contraction → pulmonary hypertension↑— Cor pulmonale

Respiratory system

PaO_2↓ (<60mmHg) →stimulate the chemoreceptors → stimulate respiratory center → strengthen respiratory movement, MV ↑, respiratory distress
PaO_2↓(<30mmHg)→inhibition of respiratory center>stimulation of respiratory center → respiratory depression
Hyperventilation→CO_2↓→inhibition of respiratory center
Severe hypoxemia → slow shallow irregular respiration or Cheyne-Stokes respiration

Haematological system

Chronic hypoxemia →stimulate hematopoiesis of bone marrow → EPO production ↑ RBC ↑

- haemoglobin saturation & O_2 Delivery capacity ↑
- blood viscosity ↑, blood stream resistance↑ → cardiac load & CO↑
- hypoxemia and blood viscosity ↑ → the risk of DIC↑

Renal & Digestive system

Renal blood vessels contraction, blood supply ↓when accompany with hypotension, DIC → Renal failure
Gastric mucosal erosion, necrosis, ulcer and bleeding
Hepatic cell impairment by hypoxia → ALT↑, jaundice

Urinary system

Mild CO2 retention →dilation of renal blood vessels → renal blood flow↑ → urine ↑
PaCO2 > 8 kPa, pH ↓↓ →renal blood vessels spasm → renal blood flow ↓
HCO3 and Na+ reabsorption↑ → urine ↓

Acid-base balance and electrolytes

Severe hypoxia → inhibition of cellular energy metabolism → insufficient energy production, production of lactic acid ↑ → sodium-potassium pump failure → metabolic acidosis, hyperkalemia → PCO_2↑
Respiratory acidosis and metabolic acidosis
pH is determined by $HCO_3/PaCO_2$ ratio
Slow CO_2 retention → compensated by kidney, decreased elimination of HCO_3^-
(It takes 1 ~ 3 days for kidney to compensate)

Clinical manifestation

Acute respiratory failure

-dyspnea
- cyanosis

Cyanosis is a typical sign of hypoxia, indicating arterial oxygen saturation lower than 90%.
The extent of cyanosis is associated with content of reduced hemoglobin. So it is less readily detectable if anemia is present and more readily seen in polycythemia.
Peripheral cyanosis is associated with stasis, in which oxyhemoglobin is reduced more than it normally is because of the prolonged peripheral blood transit time, while the PaO2 could be normal.
Central cyanosis results from arterial hypoxemia.

- Neuropsychic symptoms:
  Mental disorder, mania, coma, convulsion
- Circulatory system:
  Tachycardia, myocardial impairment, peripheral circulatory failure, hypotension, arrhythmia, cardiac arrest.
- Digestive system :
  - Hepatic function impairment: ALT↑
  - Gastrointestinal tract: mucosal erosion, stress ulcer, gastrointestinal bleeding
- Urinary system:
  Renal function impairment: BUN↑

Proteinuria, hematuria, casts in urine

Chronic respiratory failure

-Dyspnea:
Excessive respiratory effort, prolonged expiration——rapid shallow breathing——slow shallow breathing, Cheyne-Stokes breathing (CO_2 narcosis, severe respiratory depression)
- Neuropsychic symptoms:
Irritation caused by increased $PaCO_2$ in early stage: insomnia at night, drowsiness during the day
- Depression caused by pulmonary encephalopathy in late stage: apathy, convulsion, coma, tendon reflex weakened or disappear
- Circulatory system:
Peripheral vesodilation, skin congestion, warm and sweaty extremities, BP↑, CO↑, pulsus magnus, HR↑, pulsatile headache

Diagnostic criteria
History of respiratory dysfunction that severely affects the lung's ability to maintain arterial oxygenation or carbon dioxide elimination
Clinical manifestation of dyspnea and cyanosis
Blood gas analysis
- $PaO_2 < 60$ mmHg, or plus
- $PaCO_2 > 50$ mmHg

Breathing air on sea level and standard atmosphere pressure at rest
Exclude intracardiac shunt and decreased cardiac output, such as ventricular septal defect
In fact it is a pathophysiology & laboratory diagnosis

Treatment
1. Etiology Management
2. Keep airway open
Importance of airway open :
Airway obstruction: resistance ↑ → WOB↑
respiratory muscle fatigue
difficult to clear airway secretion → infection deteriorate
atelectasis → the surface area of gas exchange ↓
Complete airway obstruction → apnea, death
Clear airway secretion :
mucolytics
manual suction
Bronchodilators for patients with bronchospasm:
- β2-adrenoreceptor agonist, anticholinergic, glucocorticoid, theophylline
- Mode of administration : parenteral first and then inhale
- Mechanical ventilation+ medications delivery
- Airway humidify & nebulize

Establishing artificial airway
- Endotracheal intubation
- Tracheostomy

3. Oxygen therapy
Indications of oxygen therapy :
Pump failure: improve ventilation
Pneumonia, Pulmonary embolism, acute attack of asthma
Severe pulmonary edema, ARDS
Acute deterioration or worsening of COPD (pay attention to CO_2 retention when giving oxygen therapy!)
Inspired oxygen concentration:
Inspired oxygen concentration should be the lowest value that results in an oxygen saturation of over 90% ($PaCO_2$ about 60mmHg).

High concentrations of inspired oxygen (>35%) are safe in patients with type Ⅰ respiratory failure, as there is no risk of CO_2 retention.

While in patients with type Ⅱ respiratory failure, who are dependent on hypoxic drive for ventilation, oxygen therapy must be carefully controlled so that sufficient oxygen is supplied but without precipitating severe respiratory acidosis.

Oxygen delivery device:

1. **Nasal cannula/prongs:**

Advantage: allow patients to eat, drink, expectorate and speak

Disadvantage: FiO2 delivered is not stable and affected by breathing; high flow rates irritate nasopharyngeal mucosa

Guide: Delivers 4% Oxygen per liter flow;

FiO2 (%)=21+4×oxygen flow rate (L/min)

Flow rates should be limited to less than 7L/min.

2. **Mask:**

Simple oxygen mask, nonrebreathing mask with reservoir bag, Venturi mask.

Advantage: FiO2 delivered is comparatively stable and is adjustable; less irritative to nasopharyngeal mucosa

Disadvantage: inconvenient for patients to expectorate, eat and drink

Side effects of Oxygen therapy

- Inhibition of respiratory center in patients with type Ⅱ respiratory failure, who are dependent on hypoxic drive for ventilation → CO2 retention ↑
- Absorption atelectasis/denitrogenisation: nitrogen is replaced by more absorptive oxygen
- Oxygen poisoning : High concentrations of inspired oxygen →injury of pulmonary capillary epithelium

4. Ensure adequate alveolar ventilation, correct CO2 retention

- Respiratory stimulant
- Mechanical Ventilation

Respiratory stimulant: mainly used in CNS depression

Principles for respiratory stimulant :

Maintain potency of airway to avoid respiratory muscles fatigue and deteriorate CO2 retention

Be cautious when used in patients with frequent convulsion caused by cerebral anoxia, cerebral edema

Suitable for patients with normal respiratory muscle strength

Not suitable for patients only with oxygenation failure

Avoid sudden withdrawal

Drug: coramine, lobeline, doxapram

Non-invasive positive pressure ventilation (NIPPV)

Indications:

- Conscious and cooperative
- Stable circulation
- Be able to protect airway
- No facial trauma, injury and deformity
- Be endurable to mask

Mechanical ventilation

Indications:

- apnea;
- upper airway obstruction; impaired airway protection;
- inadequate handling of secretions;
- acute hypercapnia that is not quickly reversed by appropriate specific therapy;
- severe hypoxemia;
- progressive patient fatigue despite appropriate treatment.

5. General supportive care

- Transfer to ICU for critical care and treatment
- Infection control
- Management of electrolyte and acid-base disturbance
- Management of cor pulmonale, pulmonary encephalopathy, multi-organ dysfunction syndrome(MODS).
- Nutrition support

Acute respiratory distress syndrome (ARDS) -

A hypoxemic respiratory failure, ccharacterized by:
-Bilateral lung infiltrates
-Normal PCWP (<18 mm Hg) or no e/o LVF
-PaO2/FiO2 <200
-Multiple risk factors-

- Sepsis, aspiration, shock
- Trauma- thoracic or non-thoracic
- Multiple blood transfusions, acute pancreatitis

Management of ARDS:
Symptom- tachypnea, dyspnea
Dx- ABG- hypoxemia, CxR- B/L infiltrates
Look for other organ dysfunction
Rx-
Treat underlying disorder
Supportive mechanical ventilation- minimum PEEP & lowest FiO2 to maintain PaO2 >60 mm Hg
Maintain zero fluid balance i.e. no weight gain
Px- 30-40% mortality,~90% mortality if accompanied by sepsis

Equipment: class room, Harvey cardiopulmonary patient simulator, 6-channel ECG machine CARDIOLINE 100 L and Cardioline 200 + II S, electric pump – aspirator Medela Clario

Lesson time: 2 hours

Plan

I. Organization moments (Greeting, head count, theme announce, aim of lesson, applicants motivation for preparing for lesson).
II. Control of basic knowledges (The task source for self-knowledge skills tests from «KROK2» - additional materials, cheking workbooks)
II.1 Requirements for theoretical readiness of applicants to perform practical classes.

Requirements to knowledges:

- Definition of pulmonary insufficiency
- Modern aspects of etiology and pathophysiology of pulmonary insufficiency
- Classification of pulmonary insufficiency
- Clinical manifestation of pulmonary insufficiency
- Laboratory and instrumental investigation of pulmonary insufficiency
- Carry out differential diagnosis of pulmonary insufficiency
- Complications of pulmonary insufficiency
- Treatment, rehabilitation of patients with pulmonary insufficiency
- Prognosis and disability of patients with pulmonary insufficiency

List of didactic units

- To get a detailed anamnesis
- To do physical examination of patient, to diagnose and to estimate changes in condition
- To make a plan of additional investigation and estimate it

- Justify and make a preliminary and clinical diagnoses of pulmonary insufficiency based on severity of airflow limitation, complex evaluation of pulmonary insufficiency and make a group of patients.
- General principles and approaches to the treatment of pulmonary insufficiency
- Estimation of clinical examination, CBC, blood tests, sputum tests, pleural fluid analysis, spirometry, chest X-Ray, CT-scan, ABG and etc.

II.2 Questions (MSQ, clinical cases) for basic knowledge examination of topic

1. The leading factor of Pulmonary Insufficiency is:
A. Family history of bronchial asthma.
B. Pneumonia.
C. COPD. +
D. Long experience of working in polluted condition.
E. Long term of smoking.

2. The most common changes on spirography of the patients with COPD, complicated Chronic Cor Pulmonale are:
A. Restrictive.
B. Obstructive.
C. Mixed. +
D. All above.
E. No changes.

3. What method of investigation is used for detection SaO2 in a blood at Chronic Cor Pulmonary with Pulmonary Insufficiency?
A. Pletismography.
B. Pick-flow metry.
C. Pulsoximetry +
D. DLCO.
E. Arterial blood gases.

4. What disease, which was diagnosed 30 years ago, can lead to Chronic Cor Pulmonary with Pulmonary Insufficiency?
A. Chronic bronchitis.
B. Pleural commissure.
C. Pneumonia.
D. Bronchial asthma. +
E. Pneumosclerosis after pneumonia.

5. Choose the correct definition of Chronic Cor Pulmonary:
A. Hypertrophy or dilatation of the right heart resulting in pulmonary hypertension due to lung disease, deformity of the chest or lung vessels impression. +
B. Pneumosclerosis and respiratory system's inability to provide normal gas composition of arterial blood
C. Pathological syndrome, in which the partial pression of oxygen in arterial blood (PaO2) <60 mmHg and / or partial CO2 pression (PaCO2)> 45 mmHg.
D. Distention of air spaces located at terminal bronchioles (mostly alveolar).
E. Pathological condition where between the parietal and visceral pleura air is accumulated.

III. Proffesional skills formation (skills of patient`s management, treatment)
Professional algorithms: work with a patient (according to patients-students conversation algorithm).

During examination students must use next algorithm:

1. Nice face, smiling
2. Gentle tone of speech

3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Collecting data on patient complains, medical history, life history
5. Interpretation of clinical, laboratory and instrumental studies
6. Explanation for patient of next acting (hospitalization, workup)
7. End of conversation

Physical examination of patient with internal diseases

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Explanation of investigations are needed, taking agreement
5. Telling about possible negative feelings during investigation
6. Preparing to examination (clean warm hands, accurate nails, warm phonendoscope, screen if needed)
7. Examination (demonstration of clinical skills)
8. Interpretation of clinical, laboratory and instrumental studies
9. End of conversation

Telling to patient with internal diseases investigation results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of investigation results
5. Conversation with patient (comparing new and previous examination results, check if explanation is clear)
6. End of conversation

Planning and prognosing treatment results

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting and acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of treatment
5. Conversation with patient (explanation of features taking pills, duration of taking drugs, possible side effects)
6. Check if explanation is clear
7. End of conversation

Telling treatment prognosis

1. Nice face, smiling
2. Gentle tone of speech
3. Greeting та acquaintance, interesting in patients, showing care and respect
4. Correct and understandable for patient explanation of expected treatment results
5. Conversation with patient (explanation of importance of life-long treatment, taking medications according to list, check if explanation is clear)
6. End of conversation

Task 1

1. Collecting complains, anamnesis, examination of patients with bronchial asthma
2. Identify clinical and instrumental symptoms
3. Make a syndrome based on symptoms
4. Identify the leading clinical syndrome
5. Assign laboratory and instrumental examination (CBC, blood tests, sputum tests, pleural fluid analysis, spirometry, chest X-Ray, CT-scan, ABG and others)
6. Carry out differential diagnosis between different causes of PI
7. Make a clinical diagnosis

8. Determine a degree of disability

Task 2

Prescribing different variants of treatment according to guidelines

Task 3

Work in Internet, work with thematic literature in department library room.

Student must fill patient examination protocol (example is added).

Control materials for final part of the lesson:

The cases for self-control with standard answers.

1. The man 24 y.o. complaints of fever up to 39 ° C, dry cough, pain in the abdomen on the right side. OBJECTIVE: nasolabial triangle cyanosis, inspiratory dyspnea, participation in the act of breathing additional respiratory muscles. Percussion - shortening percussion sound. Auscultation - the weakening of breath, crackling. Respiratory rate - 60 / min, heart rate - 120 bpm. In CBC: leukocytosis, neutrophilic left shift. What is the degree of respiratory failure has a patient?

A. I
B. II
C . III
D. IV
E . 0

2. The patient 54 y.o.complains of dyspnea during mild physical exertion, cough with sputum that is difficult to depart. Objectively: diffuse cyanosis. Barrel chest. In the lungs weakened breathing with prolonged exhalation, dry whistling wheezing. Blood pressure - 140/80 mmHg. PS – 92 bpm, rhythmic. Spirography – VC 65%, FEV1 / FVC - 50%. Determine the type of pulmonary insufficiency:

A. Mixed type with prevalence of restriction.
B. Pulmonary insufficiency is absent.
C. Obstructive type.
D. Restrictive type.
E. Mixed type with prevalence of obstruction.

3. The patient 52 y.o. complains of shortness of breath, constant cough in the morning with the release of a small amount of clear sputum. From history we know that the patient smokes for 20 years. OBJECTIVE: respiratory rate - 18 / min. Box percussion sound, weakened breathing. Radiological findings: bilateral symmetrical increasing the transparency of the lung fields. Spirography: FVC - 103%, FEV1 - 72%, the index Tiffno - 62% MVL - 79%. Evaluate the results of the study:

A. Pulmonary insufficiency, restrictive type.
B. Pulmonary insufficiency, obstructive type.
C. Pulmonary insufficiency, mixed type.
D. Pulmonary insufficiency absent.
E. Is not enough data for Pulmonary insufficiency diagnosis.

4. Patients with nosocomial pneumonia observed perioral cyanosis, moderate shortness of breath, pulse to respiratory rate ratio - 2.5: 1, MLV increased, VC - reduced. Determine the degree of respiratory failure.

A. I
B. III
C. II
D. IV
E. 0

5. The patient 24 y.o. while eating suddenly feeling short of breath, anxiety, pain in the throat. Called "emergency", taken to hospital. Objectively: the patient restless, euphoric, skin moist, pale, light acrocyanosis RR 25 / min, unproductive cough, participating in breathing auxiliary muscles. In the lungs: at exhale whistling wheezing. Heart: rhythmic activity, pulse 110 bpm, blood pressure -

150/90 mmHg. The partial pressure of O2 in the blood - 70 mm Hg, CO2 35 mmHg. Highlight leading syndrome.
A. Respiratory failure.
B. Intoxication.
C. Hypertensive.
D. Heart failure.
E. Pain.
6. The patient 25 years old, suffering from asthma, complains about the lack of air sensation, shortness of breath. OBJECTIVE: moderate gravity condition expressed cyanosis and acrocyanosis, RR 36 for 1 min, whistling breath, non-productive cough, breathing in participating of auxiliary muscles; in the lungs - auscultated large number of dry whistling wheeze. Blood pressure - 140/90 mmHg, the rhythmic activity of the heart, heart rate - 110 bpm. What is the severity of Pulmonary insufficiency syndrome?
A. I.
B. II.
C. III.
D. IV.
E. None.
7. 36 y.o. patient taken to the hospital in an excited state, occasionally marked by auditory hallucinations, delusions. The wounds of the face and neck. Severe cyanosis and acrocyanosis. Breathing is rapid, shallow, with the auxiliary muscles involving, RR 36 for 1 min, rhythmic activity of the heart, Ps 130 bpm, blood pressure - 150/95 mmHg. What additional tests needed?
A. Radiography of the chest.
B. Overview of otolaryngology.
C. Determination of CO2 and O2 partial pressure.
D. The study of respiratory function.
E. Definition of central venous pressure.
8. The patient 45 y.o. brought in unconscious in the street. Determine the smell of alcohol. Skin and visible mucous are cyanotic. The neck and chest are abrasions. Breathing shallow, RR 28 for 1 min. In the lungs - crepitation in the lower, more from the right. Arrhythmic heart activity, pulse 120 bpm, blood pressure - 160/90 mmHg. ECG - sinus rhythm, regular, HR 120 bpm, ST-segment depression in leads V3-V5 up to 1 mm. What is the most likely cause of ARI?
A. Chest trauma.
B. Acute myocardial infarction.
C. Stroke.
D. Pneumonia.
E. Alcohol intoxication.
9. The patient 47 years old, suffering from bronchitis, complains of feeling shortness of breath, difficulty breathing, which appeared overnight after hypothermia, fever up to 38 ° C. OBJECTIVE: The state moderate, pronounced cyanosis and acrocyanosis, RR 26 for 1 min, dry cough, participating in breathing auxiliary muscles. In lungs: single whistling wheezing, single moist rales. HR 120 bpm, muffled heart sounds, blood pressure - 140/85 mmHg. After the treatment, which included antibacterial and bronchodilator drugs, the patient's condition improved. What are the measures of ARF prevention in this patient?
A. Avoid hypothermia, colds.
B. Constant antibiotics intake.
C. Constant bronchodilators intake.
D. Prophylactic administration of glucocorticoids.
E. Prophylactic administartion of nonsteroidal anti-inflammatory drugs.
10. 67 y.o. patient who has had a myocardial infarction 2 months ago, came to the clinic with complaints of pain in the chest during breathing, shortness of breath, subfebrile T°. OBJECTIVE: pronounced cyanosis and acrocyanosis, over lungs on both sides - a large number of small bubble

wheezing. The activity of the heart rhythmic, heart rate - 100 bpm, BP - 90/40 mm Hg. The liver stands + 5 cm under the costal arch; spleen, kidneys – are not palpable. What measures should be undertaken immediately?
A. Artificial respiration.
B. I/v administration of nitrates.
C. I/v administration of Lasix in combination with glucocorticoids.
D. Administration of potassium –keeper diuretics.
E. Administration of low molecular weight heparin.

Standard answers: 1-A, 2-E, 3-B, 4-A, 5-A, 6-B, 7-C, 8-A, 9-A, 10-C.

IV. Making conclusions, telling final marks, tasks for the next lesson

Literature list

- Basic literature source:

1. Harrison's Manual in Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 1245 p.
2. Harrison's Principles of Internal Medicine. 20th edition / Ed.by J. L. Jameson, A.S. Fauci, D.L. Kasper et al. / McGraw-Hill Education, 2020. 3528 p.

- Additional literature source:

1. International Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). Respiratory failure, not elsewhere classified, 2017 ICD-10 diagnosis code J96. 2017. http://www.icd10data.com/ (last accessed 1 June 2017).
2. GINA report, global strategy for asthma management and prevention. Updated December 2020. Evidence-based strategy for asthma management and prevention, with citations from the scientific literature.
http://www.ginasthma.org/
3. From the Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2020.

Appendix 1

An example of the initial examination of the patient

Passport part: Name, European male of 58 years old.
Complaints: shortness of breath, worsening state of breathing for the past 2 weeks.
Medical history: He has been having intermittent chronic cough for the past 3 years. The cough is productive at times. The sputum produced is mucoid in nature and about one tablespoonful in amount. There is no blood in the sputum. It is also not foul-smelling. Patient is proceeded to have shortness of breath for the past one year. The dyspnea is persistently present and described as requiring increased effort to breathe. It is worse on exertion and patient experiences reduced effort tolerance. He is now able to climb one and a half flights of stairs before becoming breathless. He has not consulted any doctors for these symptoms prior to admission.
Life history: Material and living conditions are satisfactory. Tuberculosis, venereal disease denies. No any allergic reaction to the medications. There were no occupational hazards. Hereditary history is not burdened. Patient is a chronic smoker for the past 40 years who has been smoking about twenty sticks of cigarettes a day, does not abuse alcohol. He has not left the country for the last 3 years.
Physical examination: well nourished and alert but was tachypneic. He was able to speak in sentences but there was use of his accessory muscles. There was no clubbing or cyanosis seen. There was also no peripheral edema, pallor or jaundice.
Vital signs: Pulse rate: 72 beats per minute, regular with good volume. No bounding pulse. RR: 28 breaths per minute. BP: 129/73 mm Hg. Temperature: 37 ℃. SpO2: 88%. On inspection of the

hands, there was no peripheral cyanosis or flapping tremors seen. There was also no clubbing, muscle wasting or palmar erythema seen. There was presence of nicotine stains. On inspection of the chest, there is an increased anterior posterior diameter giving rise to a barrel shaped chest. The chest moves equally with respiration and there is use of accessory muscles with intercostal, subcostal and suprasternal retraction. There are no chest wall deformities. On palpation, chest expansion is reduced on both sides. Tactile fremitus is equal on both sides. On percussion, there is hyperresonance over both lungs with loss of liver and cardiac dullness. On auscultation vesicular breathing is heard. There is generalized expiratory rhonchi. There is also fine early inspiratory crepitations heard at the lower zones of both lungs. The apex beat could not be palpated. There were no parasternal heaves or thrills palpable. On auscultation, normal first and second heart sounds were heard. There was mild bilateral pitting edema. Examination of the abdomen:
On inspection, the abdomen is flat and moves with respiration. There was no guarding or tenderness. The liver and spleen were not palpable. There was no organomegaly. Examination of the neurological system was normal.

Plan of investigation:

1) Full Blood Count

Justification: In order to view the total white count as well as the differential count to see if there is an infection which has caused this episode of exacerbation. There may also be secondary polycythemia if the patient has chronic pulmonary hypertension.
Results:
White cell count : 7.91 X 109/L
Red blood cell : 4.48 X 1012/L
Haemoglobin : 133.00 g/dl
Haematocrit : 42.00 ratio
Mean cell volume : 93.80 fL
Mean cell haemoglobin : 29.70 pg
Mean cell haemoglobin conc. : 317.00 g/l
Platelets : 141.00 X 109/L
Differential count
Neutrophils : 60.10% 4.76 X 109/L
Lymphocytes : 25.30% 2.00 X 109/L
Monocytes : 13.80% 1.09 X 109/L
Eosinophils : 0.50% 0.04 X 109/L
Basophils : 0.30% 0.02 X 109/L
Interpretation: This is a normal full blood count result with normal total white count as well as normal haemoglobin levels.

2) Plain chest radiograph

Justification: Done in order to look for evidence of chronic obstructive airway disease such as hyperinflated chest or evidence of congestive cardiac failure such as cardiomegaly and prominent upper lobe vessels.
Results: Hyperinflation of the chest with the 7th anterior rib crossing the diaphragm. No other abnormalities seen.
Interpretation: Hyperinflation of the lung fields is consistent with the provisional diagnosis of chronic obstructive airway disease.

3) Sputum FEME, culture and sensitivity (not done)

Justification: In order to look for any bacteria which may have been the cause of the exacerbation . If there any organism cultured, proper antibiotics can be given based on the sensitivity test.

4) Blood urea serum electrolytes and creatinine

Justification: To look for renal impairment which may be present due to Mr TLT having hypertension. Renal impairment may also affect the dosage and type of antibiotics used.
Results:
Urea : 3.7mmol/L

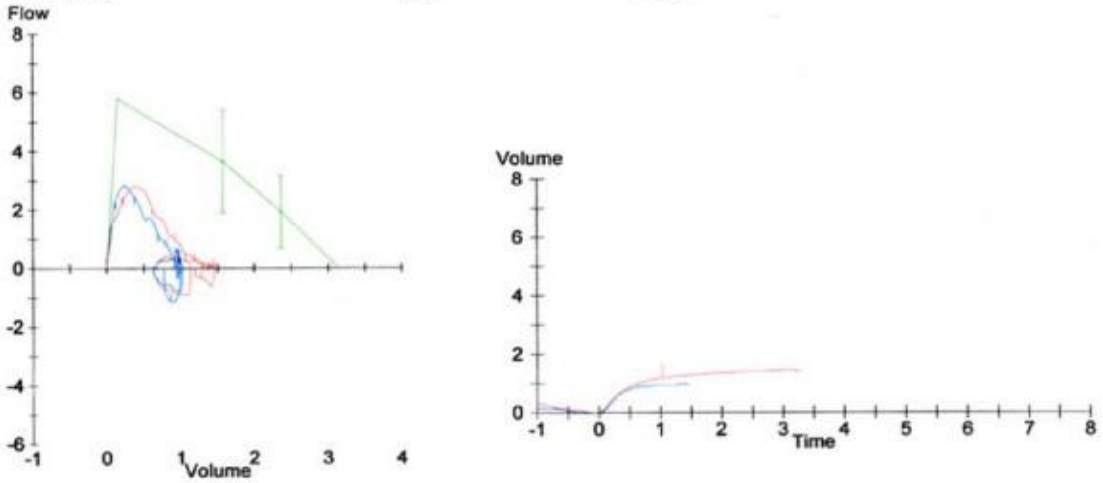
Sodium : 135 mmol/L
Potassium : 3.7 mmol/L
Creatinine : 65 umol/L
Interpretation: Normal result. There is no renal impairment

5) Electrocardiogram

Justification: To look for evidence of right ventricular hypertrophy or right atrial hypertrophy which may be seen in chronic lung disease.
Results: ECG with sinus rhythm. There is no P pulmonale seen. There is low voltage seen. No ischaemic changes seen. No left ventricular hypertrophy.
Interpretation: Normal ECG with low voltage is seen in a hyperinflated chest such as in patients with COPD

6) Spirometry

Spirometri		Ref	Pre Meas	Pre % Ref	Post Meas	Post % Ref	Post % Chg
FVC	Liters	3.16	1.01	32	1.47	47	46
FEV1	Liters	3.01	0.96	32	1.21	40	26
FEV1/FVC	%	86	95		82		
FEF25%	L/min		162		158		-2
FEF50%	L/min	220	134	61	112	51	-16
FEF75%	L/min	117	62	53	30	26	-51
FEF25-75%	L/min	204	108	53	79	39	-27
PEF	L/min	349	172	49	171	49	-1
FIVC	Liters	3.16	0.23	7	0.27	8	17
FVL Time			12:17		12:39		



Diagnosis: COPD, group C, chronic pulmonary insufficiency

Acute management

1. Provide supplemental oxygen via nasal prong 3L/min and maintain SpO2 above 90%. Arterial blood gas should be done in order to ensure adequate oxygenation without carbon dioxide retention of acidosis.
2. Close monitoring of vital signs and SpO2 hourly until the patient's breathlessness improves. Nursing staff to inform if patient deteriorates such as increased respiratory rate or drop in oxygen saturation below 92%.
3. Give nebulization of Ipratropium Bromide:Salbutamol:Normal Saline in ratio of 2:2:1 every four hours until breathlessness decreases.
4. Oral prednisolone 40mg once daily for 10 days
5. Postural drainage and chest physiotherapy may be performed.

Long term management

1. Salmeterol 50 mcg in inhaler
2. Flutikazon 500 mcg in inhaler
3. Counseling on proper inhaler technique.

4. Counseling on smoking cessation.

Practical lesson #18
Theme: Gastroesophageal reflux disease.

2. Goal:
To study:
- etiology, pathogenesis, classification, clinic, complications, diagnosis and treatment of GORD;
- classification of antisecretory, prokinetic drugs and antacids;
- general and dietary recommendations, duration of treatment with endoscopic-negative GORD and reflux- esophagitis. Methods for monitoring the effectiveness of treatment;
- general principles of endoscopic and surgical treatment of Barrett's esophagus and GORD.

3. Basic concepts. GERD: definition, epidemiology, aetiology, pathophysiology. Classification of GERD. Step-by-step diagnostic approach. Risk factors of GERD. Diagnostic tests. Diagnostic criteria. Differential diagnostics. Step-by-step treatment approach. Emergency treatment. Complications. Prognosis. Treatment guidelines.

GERD is defined as symptoms or complications resulting from the reflux of gastric contents into the [o]esophagus or beyond, into the oral cavity (including larynx) or lung'.

Typical symptoms are heartburn and acid regurgitation. Atypical symptoms include cough, laryngitis, asthma, or dental erosion. GORD may occur with or without oesophageal inflammation (oesophagitis). Symptoms may be without erosions on endoscopic examination (non-erosive reflux disease or NERD), or with erosions present (ERD)

Incompetence of the lower esophageal sphincter allows reflux of gastric contents into the esophagus, causing burning pain. Prolonged reflux may lead to esophagitis, stricture, and rarely metaplasia or cancer. Diagnosis is clinical, sometimes with endoscopy, with or without acid testing. Treatment involves lifestyle modification, acid suppression using proton pump inhibitors, and sometimes surgical repair.

Montreal definition

This classifies oesophageal syndromes.

1. Syndromes with symptoms and no injury:
    - Typical reflux syndrome
    - Reflux chest pain syndrome.
2. Syndromes with oesophageal injury:
    - Reflux oesophagitis
    - Reflux stricture
    - Barrett's oesophagus
    - Oesophageal adenocarcinoma.
3. Extra-oesophageal syndromes
    3.1. Established associations:
    - Reflux cough syndrome
    - Reflux laryngitis syndrome
    - Reflux asthma syndrome
    - Reflux dental erosion syndrome.

    3.2. Proposed associations:
    - Pharyngitis
    - Sinusitis
    - Idiopathic pulmonary fibrosis

- Recurrent otitis media.

Etiology

The presence of reflux implies lower esophageal sphincter (LES) incompetence, which may result from a generalized loss of intrinsic sphincter tone or from recurrent inappropriate transient relaxations (ie, unrelated to swallowing). Transient LES relaxations are triggered by gastric distention or subthreshold pharyngeal stimulation.

Factors that contribute to the competence of the gastroesophageal junction include the angle of the cardioesophageal junction, the action of the diaphragm, and gravity (ie, an upright position). Factors contributing to reflux include weight gain, fatty foods, caffeinated or carbonated beverages, alcohol, tobacco smoking, and drugs. Drugs that lower LES pressure include anticholinergics, antihistamines, tricyclic antidepressants, Calcium channel blockers, progesterone, and nitrates.

Symptoms and Signs

The most prominent symptom of GORD is heartburn, with or without regurgitation of gastric contents into the mouth. Infants present with vomiting, irritability, anorexia, and sometimes symptoms of chronic aspiration. Both adults and infants with chronic aspiration may have cough, hoarseness, or wheezing.

Esophagitis may cause odynophagia and even esophageal hemorrhage, which is usually occult but can be massive. Peptic stricture causes a gradually progressive dysphagia for solid foods. Peptic esophageal ulcers cause the same type of pain as gastric or duodenal ulcers, but the pain is usually localized to the xiphoid or high substernal region. Peptic esophageal ulcers heal slowly, tend to recur, and usually leave a stricture on healing.

Diagnosis

TEST	**RESULT**
proton-pump inhibitor (PPI) trial	symptom improvement
Further tests are indicated if symptoms do not improve with therapeutic 8-week trial of a PPI or if patient has alarm symptoms.	may show oesophagitis
oesophagogastroduodenoscopy (OGD)	(erosion, ulcerations,
• Indicated for alarm symptoms or symptoms suggesting complicated disease (atypical, persistent, or relapsing symptoms).	strictures) or Barrett's
• Normal findings on endoscopy can occur with GORD (i.e., nonerosive reflux disease [NERD]).Routine biopsies are not recommended by guidelines.	oesophagus
• Evidence is conflicting as to whether frequency and severity of symptoms can predict Barrett's oesophagus, severity of oesophagitis, or other complications.	pH <4 more than 4% of the
• Higher grades of erosive oesophagitis may be associated with the finding of Barrett's oesophagus with healing. Thus, if endoscopy is performed to diagnose GORD, it may best be performed off therapy.	time is abnormal
If performed because of concern for Barrett's oesophagus (e.g., longstanding symptoms), it may be best to carry out the procedure during treatment.	may suggest achalasia,

Complications

GERD may lead to esophagitis, peptic esophageal ulcer, esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma. Factors that contribute to the development of esophagitis include the caustic nature of the refluxate, the inability to clear the refluxate from the esophagus, the volume of gastric contents, and local mucosal protective functions. Some patients, particularly infants, aspirate the reflux material.

Treatment

Head of bed elevated.

Coffee, alcohol, fats, and smoking avoided.

Proton pump inhibitors.

Management of uncomplicated GERD consists of elevating the head of the bed about 15 cm (6 in) and avoiding the following: eating within 2 to 3 h of bedtime, strong stimulants of acid secretion (eg, coffee, alcohol), certain drugs (eg, anticholinergics), specific foods (eg, fats, chocolate), and smoking.

Drug therapy is with a proton pump inhibitor. For example, adults can be given esomeprazole 40 mg 30 min before breakfast. In some cases, proton pump inhibitors may be given bid. These drugs may be continued long-term, but the dose should be adjusted to the minimum required to prevent symptoms. H2 blockers (eg, ranitidine 150 mg at bedtime) or promotility agents (eg, metoclopramide
10 mg 30 min before meals and at bedtime) are less effective.

Antireflux surgery (usually via laparoscopy) is done on patients with serious esophagitis, large hiatal hernias, hemorrhage, stricture, or ulcers. Esophageal strictures are managed by repeated balloon dilation.

Barrett's esophagus may or may not regress with medical or surgical therapy. Because Barrett's esophagus is a precursor to adenocarcinoma, endoscopic surveillance for malignant transformation is recommended every 1 to 2 yr. Surveillance has uncertain cost-effectiveness in patients with low-grade dysplasia but is important in high-grade dysplasia in patients who are unable to undergo surgical resection. Alternatively, Barrett's esophagus may be treated with endoscopic mucosal resection, photodynamic therapy, cryotherapy, or laser ablation.

4. Equipment: study room, acknowledge with protocol and procedure of fibrogastroduodenoscopy and results interpretation during visit to functional department (1st floor in University Clinic).

5. Learning hours: 2 hours.

Plan of the lesson

I. Organizational moment (greetings, checking who is present on the lesson, announcing topic and goal of the lesson, motivating applicants to study the topic).

II. Control of basic knowledge (oral questioning, tests, checking of how clinical cases and workbooks are fulfilled).

2.1. Demands for applicants theoretical preparation

Applicants should know:

1) GERD definition.
2) GERD epidemiology, aetiology and pathogenesis..
3) GERD classification.
4) Clinical manifestions of GERD.
5) GERD diagnostics.
6) Differential diagnostics of GERD.
7) GERD complications.
8) Standarts of treatment for GERD.
9) GERD prevention.
10) GERD complications.

Didactic units list:
- interview the patient with detailing complaints, identify main symptoms and syndromes of GERD;
- conduct patient's physical examination, to reveal and estimate abnormal changes;
- perform investigation methods used in GERD, point indications for their use and the diagnostic value;
- interpret the results of investigation: oesophagogastroduodenoscopy, ambulatory PH-monitoring, esophageal manometry, barium swallow test;
- substantiate and formulate preliminary and final clinical diagnosis based on results of diagnostic tests;
- correctly choose regimen of treatment, depending on the specific clinical situation;
- to be acknowledged with last updated diagnostic and treatment guidelines.

Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Tests for self-control

1. The reason of GERD may be:
A. Dolichocolon.
B. Hernia of esophageal diaphragm hole. +
C. Overdose of antacids.
D. Lack of fiber in food.
E. All of above.
2. What is not a GERD complication?
A. Bleeding.
B. Esophageal adenocarcinoma.
C. Stricture.
D. Acute intestinal obstruction. +
E. Erosion of esophageal mucous.
3. What degree of reflux esophagitis if : one (or more) erosion longer than 5 mm, limited by the boundaries of one fold?
A. A.
B. B. +
C. C.
D. D.
E. E.
4. Which drugs do not block the secretion of hydrochloric acid?
A. Famotidine.
B. Rabeprazole.
C. Atropine. +
D. Maalox.
E. Gastrocepine.
5. Which method is not informative in the GERD diagnosis?
A. PPI-test.
B. Upper endoscopy.
C. CT. +
D. impedance -metry.
E. Complete blood count.
6. Famotidine is:
A. Prokinetic.
B. Antacid.
C. H_2 -receptor histamine blockers. +
D. Peripheral M-cholinolitics.

E. Antiviral drug
7. In the treatment of duodenogastral reflux in GERD you can include:
A. H2 blocker at night. +
B. Enzyme preparations.
C. Ursodeoxycholic acid.
D. Laxatives drugs.
E. Probiotics.
8. What method of diagnosis is optimal as a screening for GERD?
A. PPI-test +
B. Upper endoscopy.
C. X-ray.
D. Ultrasound.
E. ECG.
9. What PPI is used for faster achievement acid-inhibitor effect, sufficient for GERD ?
A. Esomeprazole. +
B. Pantoprazole.
C. Rabeprazole.
D. Lanzoprazol.
E. Omeprazole
10. Patient, 42 y.o. Complaints: difficulty in swallowing food, pain in the lower part of the sternum, sometimes at night with food regurgitation, which is eaten in the evening. Lost weight over 4 months to 2 kg. On examination revealed no pathology. On ECG - a slight depression of ST segment in III lead. X-ray: esophageal peristalsis is absent, a significant expansion of the esophagus to the cardiac department, where the esophagus is narrowed in the form of the beak. A blood test – normal. Your diagnosis?
A. Achalasia of the esophagus.
B. Cancer of the esophagus.
C. Sclerodermia with esophagitis.
D. Esophagus diverticulum.
E. Diaphragmatic hernia. +
III. Formation of professional skills, abilities:

3.1. content of tasks (tasks, clinical situations, etc.)

Case history.

A 42-year-old woman has heartburn after meals and a sour taste in her mouth. For the past 4 to 6 months she has had symptoms several times per week. Symptoms are worse when she lies down or bends over. Antacids help somewhat. The patient has no dysphagia, vomiting, abdominal pain, exertional symptoms, melaena, or weight loss. Past medical history and family history are non-contributory. The patient drinks alcohol occasionally and does not smoke. On physical examination, height is 1.63 m (5 feet 4 inches),weight 77.1 kg, and BP 140/88 mmHg. The remainder of the examination is unremarkable.

3.2. recommendations (instructions) for performing tasks (professional algorithms, orientation maps for the formation of practical skills, etc.)

Professional algorithms.

I. Patient's examination.

During patient's examination students should keep such communicative skills:
1. Friendly face expression.
2. Kind voice tone.

3. Greetings, showing concern and respect about the patient.
4. Find out patient's complaints and anamnesis .
5. Explanation of investigation results.
6. Explanation of specific actions (hospitalization, carrying out investigations) which are planned to be performed in the future.
7. Finishing of the talk.

II. Patient's examination and investigation algorithm.

1. Diagnosis is clinical, supported by testing when required. Heartburn and regurgitation are the most reliable symptoms.
2. A short trial (8 weeks) of PPIs and lifestyle therapy (such as weight loss if needed, and elevation of head of bed for nocturnal features) should be started in patients with typical symptoms.
3. Upper endoscopy (oesophagogastroduodenoscopy) is indicated in patients with atypical, relapsing or persistent symptoms.
4. Patients with persistent symptoms on therapy with PPIs and unrevealing endoscopy undergo further testing: manometry next to evaluate oesophageal contractions and lower oesophageal sphincter function. Also ambulatory
reflux (pH or impedance-pH) monitoring test.
5. It should be explained to patient which investigation will be held and indications for this investigation.
6. A doctor should receive patient's agreement on investigation.
7. A doctor should warn patient about possibilities of unpleasant feelings during oesophagogastroduodenoscopy.
8. Results of investigation should be explained to a patient.

III. Step-by-step algorithm of treatment.

1. A patient should informed be about necessity of the prescribed treatment.
2. Dosages, drugs intake regimens, duration of treatment, side effects of the prescribed therapy should be kindly explained to patient.
3. Most patients with GORD require prolonged pharmacotherapy with acid suppressants and proton pump inhibitors are the most effective drugs in this category.
4. For patients <40 years old who have typical, regular heartburn and no alarm symptoms, treatment should be started with standard-dose PPIs for about 8 weeks. It is recommended to start treatment with the lowest effective dose of PPI.
5. Lifestyle changes are recommended for all patients. These include: weight loss for overweight people; smoking cessation for tobacco smokers; head-of-bed-elevation and avoidance of late-night eating if nocturnal symptoms are present.
6. Bedtime adjunctive use of H2 antagonists may be considered in people with nocturnal symptoms or pH-monitoring evidence of nocturnal oesophageal acid reflux, when PPIs are not completely effective.
7. Patients who present with complicated or atypical GORD (e.g., dysphagia or evidence of GI bleeding) usually have immediate endoscopy. These patients should also be treated with PPIs.
8. People with non-erosive reflux disease may be able to use on-demand or intermittent PPI therapy.
9. Surgery (open or laparoscopic fundoplication) is reserved mainly for people who have had a good response to PPIs but who do not wish to take long-term medical treatment.
10. Patients should be involved in the decision to initiate surgery, as evidence for surgery is conflicting.

3.3. requirements for students work results.

As a results of studying students must perform the following:
-possess skills of communication and clinical examination of a patient with GERD;

-collect data on patient complaints, medical history, life history;
-evaluate information about the diagnosis of GERD using a standard procedure, based on the results of laboratory and instrumental studies. Determine the list of required clinical, laboratory and instrumental studies and evaluate their results;
- identify the leading clinical symptom or syndrome. Establish the most probable or syndrom diagnosis GERDS. Assign laboratory and instrumental examination of the patient. Carry out differential diagnosis of GERD. Establish preliminary and clinical diagnosis;
- determine the principles of treatment, the required regime of work/rest and alimentary regime of patients with GERD;
- diagnose emergencies in the clinic of GERD;
- define tactics and provide emergency medical care;
- perform an expertise of work capacity of patients with GERD.

3.4. control materials for the final stage of the lesson.

Materials for self- training quality.

A. Review Questions.

1. Definition of GERD.
2. Etiology and pathogenesis of GERD.
3. Classification by ICD-10 and clinical classification of GERD.
4. Typical and atypical symptoms of GERD.
5. Stages of diagnosis in accordance with modern standards of medical care.
6. The program of differential diagnosis.
7. Principles of treatment to modern standards of rendering medical care.
8. Principles of the management in the patients with GERD.

B. Work 1

1. Collection of complaints, anamnesis, examination of a patient with GERD.
2. Detection of clinical and instrumental symptoms.
3. Grouping symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data (clinical analysis of blood, urine, biochemical analysis of blood, PPI - test, radiography of the esophagus and stomach with barium, FGDS, ECG, echocardiography, etc.).
6. Carrying out a differential diagnosis.
7. Formulation of the clinical diagnosis.
8. Write a prescription list for patients diagnosed with GERD, which would include diet and prescribed drugs.
9. Determining of the disability degree.

Work 2.

Assignment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the department library with thematic literature.
The student fills in the protocol of the patient's examination. An example of the initial examination of the patient is attached.

C. The tests for self-control with standard answers.

1. A 38 y.o. man complains of having occasional problems with swallowing of both hard and fluid food for many months. Sometimes he feels intense pain behind his breast bone, epecially after hot drinks. There are asphyxia onsets at night. He has not put off weight. Objectively: his general

condition is satisfactory, skin is of usual colour. Examination revealed no changes of gastrointestinal tract. X-ray picture of thorax organs presents esophagus dilatation with level of fluid in it. What is the preliminary diagnosis?

A Oesophagus achalasia
B Myastenia
C Cancer of oesophagus
D Esophagus candidosis
E Gastroesophageal reflux

2. A 49-year-old patient complains of deglutition problems, especially with solid food, hiccups, voice hoarseness, nausea, regurgitation, significant weight loss (15 kg within 2,5 months). Objectively: body weight is reduced. Skin is pale and dry. In lungs: vesicular breathing, heart sounds are loud enough, heart activity is rhythmic. The abdomen is soft, painless on palpation. Liver is not enlarged. What study is required to make a diagnosis?

A Clinical blood test
B Esophageal duodenoscopy along with biopsy
C X-ray of digestive tract organs
D X-ray in Trendelenburg's position
E Study of gastric secretion

3. A male patient complains of heartburn which gets stronger while bending the body, retrosternal pain during swallowing. There is a hiatus hernia on X-ray. What disorder should be expected at gastroscopy?

A Gastric peptic ulcer
B Chronic gastritis
C Gastroesophageal reflux
D Acute erosive gastritis
E Duodenal peptic ulcer

4. A 35-year-old patient complains of heartburn, sour eructation, burning, compressing retrosternal pain and pain along the esophagus rising during forward bending of body. The patient hasn't been examined, takes Almagel on his own initiative, claims to feel better after its taking. Make a provisional diagnosis:

A Gastric ulcer
B Functional dyspepsia
C Cardiospasm
D Gastroesophageal reflux disease
E Duodenal ulcer

5. A patient complains of retrosternal pain, difficult swallowing, over 10 kg weight loss within three months, general weakness. In blood: hypochromic anaemia, neutrophilic leukocytosis. In feces: weakly positive Gregersen's reaction. On esophagram a filling defect with ill-defined serrated edges shows up along a large portion of the oesophagus. What is the most likely diagnosis?

A Sideropenic dysphagia
B Benign tumour
C Esophageal achalasia
D Peptic ulcer
E Esophageal carcinoma

6. A patient suffering from gastroesophageal reflux has taken from time to time a certain drug that "reduces acidity" over 5 years. This drug was recommended by a pharmaceutist. The following side effects are observed: osteoporosis, muscle asthenia, indisposition. What drug has such following effects?

A Aluminium-bearing antacid
B Inhibitor of proton pump
C H2-blocker
D Metoclopramide

E Gastrozepin

7. A 35-year-old man complains on chest pain for several months, occasionally having a bitter taste in the mouth. The pain is localized behind the chest, occurs at rest and sometimes radiates to the neck, does not increase with exercise, may increase after alcohol and large amounts of food. Occasionally there is a dry cough and hoarseness. The condition worsens at night. Swallowing is not disturbed, body weight is increased. No changes detected during examination. What is the most likely diagnosis?

A. Chronic pharyngitis
B. Esophageal cancer
C. Bronchial asthma
D. GORD
E. Hysteria

8. In 22-year-old patient during fall appeared pain in the right epigastrium, which occurs 1.5-2 hours after eating and at night. He complains on heartburn, constipation. The pain is aggravated by eating spicy, salty and sour food, decreases after Na-hydrocarbonate usage and after putting a warm bag on the "painful place". Ill for a 1 year. Objectively: on palpation of the abdominal organs there is pain in the epigastrium on the right side, in the same area - a slight resistance of the abdominal muscles. Which disease is most likely?

A. Diaphragmatic hernia
B. Gastroesophageal reflux disease
C. Chronic pancreatitis
D. Peptic ulcer of the stomach
E. Peptic ulcer of the duodenum

9. A 48-year-old woman complains of a feeling of compression in the esophagus, palpitations, difficulty breathing when eating solid foods; sometimes vomiting with a full mouth, at night - a symptom of a "wet pillow". Ill for about 6 months. Objectively: t - 36.5 C, height - 168 cm, weight - 72 kg, pulse - 76 beats / min., blood pressure - 120/80 mm Hg. Radiologically: the esophagus is significantly dilated, in the cardiac part - narrowed. What pathology most likely caused dysphagia in the patient?

A. Achalasia of the cardia
B. Primary esophagospasm
C. Hernia of the esophageal lumen of the diaphragm
D. Esophageal cancer
E. Gastroesophageal reflux disease

10. A 41-year-old patient complains of epigastric pain after exercise, heartburn, prolonged hiccups, increased salivation. Laboratory: signs of hypochromic anemia, positive reaction on occult blood in feces. X-ray of the stomach in the position of Trendelenburg shows passing of barium mixture into the cardiac part of the stomach, which is located in the chest. Which diagnosis is most likely?

A Hernia of the esophageal lumen of the diaphragm
B Gastritis with reduced acid function of the stomach
C Gastroesophageal reflux disease
D Peptic ulcer disease
E Duodenogastric reflux

11. The patient complains of heartburn, which is exacerbated while bending forward, chest pain during swallowing. The presence of GERD is suspected. Which of the research methods should be used to confirm the diagnosis?

A. Fibrogastroscopy
B. Computed tomography of the thoracic cavity
C. Outpatient impedance-pH monitoring
D. A and C
E. All the abovementioned

12. A patient with gastroesophageal reflux disease for 5 years periodically, on the recommendation of a pharmacist, takes a drug "reducing acidity". The following side effects occurred: osteoporosis, muscle weakness, malaise. What drug has such a side effect?
A. Metoclopramide
B. Rabeprazole
C. Almagel
D. Gastrocepin
E. Famotidine
13. The 58-year-old patient complains of heartburn, belching, which are aggravated by bending forward, pain when swallowing behind the sternum. Fibrogastroscopic investigation revealed Barrett's esophagus. By what can be complicated this pathology?
A. Gastric dyspepsia
B. Esophageal cancer
C. Gastric ulcer
D. Erosive gastritis
E. Duodenal ulcer
14. A 55-year-old patient complains on heartburn, which is exacerbated by bending forward, chest pain when swallowing. X-ray investigation revealed a hernia of the esophageal lumen of the diaphragm. GERD was established during fibrogastroscopy. Concomitant pathology - hypertension, constantly taking amlodipine. Direction of treatment?
A. Prescribe pantoprozole
B. Prescribe domperidone
C. Replace amlodipine with another antihypertensive
D. All of the abovementioned
E. None of the abovementioned

Standard answers: 1-A, 2-B, 3-C, 4-D, 5-E, 6-A, 7-D, 8-E, 9-A, 10-A, 11-D, 12-C, 13-B, 14-D.

Information necessary for the formation of knowledge-skills can be found in:

- Basic literature source:
1. Gyawali CP, Kahrilas PJ, Savarino E, et al. Modern diagnosis of GERD: the Lyon Consensus. Gut 2018; 67:1351-62. doi:10.1136/gutjnl-2017-314722 pmid:29437910
2. Sandhu D.S., Fass R. Current Trends in the Management of Gastroesophageal Reflux Disease / Gut Liver, 2018 Jan; 12(1): 7–16.

- Additional literature source:
1. Eusebi LH, Ratnakumaran R, Yuan Y, Solaymani-Dodaran M, Bazzoli F, Ford AC. Global prevalence of, and risk factors for, gastro-oesophageal reflux symptoms: a meta-analysis. Gut 2018; 67:430-40. doi:10.1136/gutjnl-2016-313589 pmid:28232473

Appendix 1

Example of the primary examination of the patient

Passport data: name and surname, age

Complaints:

Burning pain, which is localized behind the sternum, do not have a clear connection with exercise and occur immediately after eating, the pain does not pass after taking nitroglycerin (which the patient has taken by himself); as well as heartburn, heaviness and fullness in the epigastric region after eating, belching with air and eaten food.

Anamnesis morbi

The patient ill for 6 months, previously did not look for medical help, was not examined.

Anamnesis vitae

Living conditions are satisfactory. Botkin's disease, tuberculosis, sexually transmitted diseases, malaria denies.

Professional anamnesis: not burdened.

Hereditary history is not burdened.

Pave not been in contact with infectious patients for the last 3 days. He has not left the country in the last 3 years.

***Hereditary history**: not burdened*

Neurological history

At the time of examination signs of focal neurological symptoms were not detected.

***Allergic history**: not burdened*

Epidemiology

Tuberculosis, malaria, viral hepatitis, Botkin's disease, veneral disease, HIV, AIDS, pediculosis – denies.

***Oncoanamnesis**: denies.*

***Insurance anamnesis**: There is no need to issue a seak leave, for the last 12 months a seak leave document has not been issued in this regard.*

***Postponed operations**: denies.*

***Bad habits**: smokes for 20 years, 1 pack a day*

Examination of organ systems:

GENERAL Condition: satisfactory

CONSCIOUSNESS: clear

Body shape: hyperstenic

Fatness: high nutrition

POSITION OF THE PATIENT: active

BODY TEMPERATURE: 36.6 C. Signs of alcohol intoxication - no

SKIN: Skin of normal color, clean. Tissue turgor is normal. Skin pigmentation: depigmentation - no. Rash: no; other changes in the skin: no.

Visible mucous membranes: Normal color

LYMPH NODES: not enlarged

THYROID GLAND: no pathology

Oncological examination was performed, no visual forms of oncopathology were detected

Cardiovascular system:

PERCUSSION OF THE HEART: the limits of relative cardiac dullness: right on the right edge of the sternum, upper -III rib on the left parasternalis line, left - 2 cm outward from the left mediaclavicularis line in the V intercostal space

HEART activity: rhythmic, heart rate - 74 per 1 min. Pulse 74 in 1 min. Heart tones: muffled

HEART MURMURS: no

EDEMA: no

BP 125 / 85 mm Hg

EXAMINATION OF ARTERIES: no pathology

VEIN STUDY: no pathology

RESPIRATORY SYSTEM:
BREATHING: no dyspnea at rest, RR 16 in 1 min.
Sputum: no
CHEST: cylindrical, not deformed. Intercostal spaces: NOT smoothed. Participation of additional muscles: no, RR – 16 in 1 min. SpO2 = 98%
Percussion over the lungs: clear lung sound.
PULMONARY AUSCULTATION: vesicular breathing over both lungs. Pleural friction noise - no
DIGESTIVE SYSTEM:
TONGUE: wet; covered with white plaque
Tonsils: not enlarged
STOMACH: participates in the act of breathing. No hernia. Pulsation in the epigastrium - no. There is no dilation of the subcutaneous veins
Palpation: moderately painful in the epigastric region
Pathological symptoms: not detected
Liver: not enlarged
Gallbladder: not palpable
Pancreas: painless
Spleen: not palpable,
PERCUTIONAL SOUND OVER THE ABDOMINAL CAVITY: unchanged,
FECES: normal, no pathological impurities
URINARY SYSTEM:
Palpation of the kidneys: not palpable
Pasternatsky's symptom is negative on both sides.
Urination: free, painless, frequency per day: 3-4 times.
Urinary incontinence: no.
SENSES:
SIGHT: not violated (OU). There is no other pathology
HEARING: normal, no deafness, pain: no. Tinnitus: no.
Musculoskeletal system:
Pathology of the musculoskeletal system was not detected
On the basis of complaints, anamnesis, objective examination, it is possible to make a preliminary diagnosis:
GERD
Plan of investigation
general blood test, general urine test, glycemia level (8.00, 13.00, 17.00, 21.00)
Biochemistry: liver tests, glucose, transaminases, protein, lipid spectrum, coagulogram, amylase, AF, LDG, GGT, CPK, serum iron, potassium, CRP, seromucoid, RF, ASLO.
ECG, FGDS with biopsy, helpil-test, ultrasound of abdominal organs
Consultation with a neurologist, cardiologist, gastroenterologist.
Treatment plan
Normalization of lifestyle
Drug therapy:
- Omeprazole 20 mg - 1 tab. x 2 times/day, 20 minutes before eating
- Motilium 10 mg - 1 tab. x 3 times/day, 20 minutes before eating
- Almagel - 1 pack. during heartburn
- Eradication of Helicobacter pylori if there is a positive helpil test

Appendix 2

Tests of basic knowledge level in KROK format

Theme 18. Gastroesophagel reflux disease

1. A 35-year-old man complains on chest pain for several months, occasionally having a bitter taste in the mouth. The pain is localized behind the chest, occurs at rest and sometimes radiates to the neck, does not increase with exercise, may increase after alcohol and large amounts of food. Occasionally there is a dry cough and hoarseness. The condition worsens at night. Swallowing is not disturbed, body weight is increased. No changes detected during examination. What is the most likely diagnosis?
A. Chronic pharyngitis
B. Esophageal cancer
C. Bronchial asthma
D. GORD
E. Hysteria
2. In 22-year-old patient during fall appeared pain in the right epigastrium, which occurs 1.5-2 hours after eating and at night. He complains on heartburn, constipation. The pain is aggravated by eating spicy, salty and sour food, decreases after Na-hydrocarbonate usage and after putting a warm bag on the "painful place". Ill for a 1 year. Objectively: on palpation of the abdominal organs there is pain in the epigastrium on the right side, in the same area - a slight resistance of the abdominal muscles. Which disease is most likely?
A. Diaphragmatic hernia
B. Gastroesophageal reflux disease
C. Chronic pancreatitis
D. Peptic ulcer of the stomach
E. Peptic ulcer of the duodenum
3. A 48-year-old woman complains of a feeling of compression in the esophagus, palpitations, difficulty breathing when eating solid foods; sometimes vomiting with a full mouth, at night - a symptom of a "wet pillow". Ill for about 6 months. Objectively: t - 36.5 C, height - 168 cm, weight - 72 kg, pulse - 76 beats / min., blood pressure - 120/80 mm Hg. Radiologically: the esophagus is significantly dilated, in the cardiac part - narrowed. What pathology most likely caused dysphagia in the patient?
A. Achalasia of the cardia
B. Primary esophagospasm
C. Hernia of the esophageal lumen of the diaphragm
D. Esophageal cancer
E. Gastroesophageal reflux disease
4. A 41-year-old patient complains of epigastric pain after exercise, heartburn, prolonged hiccups, increased salivation. Laboratory: signs of hypochromic anemia, positive reaction on occult blood in feces. X-ray of the stomach in the position of Trendelenburg shows passing of barium mixture into the cardiac part of the stomach, which is located in the chest. Which diagnosis is most likely?
A Hernia of the esophageal lumen of the diaphragm
B Gastritis with reduced acid function of the stomach
C Gastroesophageal reflux disease
D Peptic ulcer disease
E Duodenogastric reflux.
5. The patient complains of heartburn, which is exacerbated while bending forward, chest pain during swallowing. The presence of GERD is suspected. Which of the research methods should be used to confirm the diagnosis?
A. Fibrogastroscopy
B. Computed tomography of the thoracic cavity
C. Outpatient impedance-pH monitoring

D. A and C
E. All the abovementioned
6. A patient with gastroesophageal reflux disease for 5 years periodically, on the recommendation of a pharmacist, takes a drug "reducing acidity". The following side effects occurred: osteoporosis, muscle weakness, malaise. What drug has such a side effect?
A. Metoclopramide
B. Rabeprazole
C. Almagel
D. Gastrocepin
E. Famotidine
7. The 58-year-old patient complains of heartburn, belching, which are aggravated by bending forward, pain when swallowing behind the sternum. Fibrogastroscopic investigation revealed Barrett's esophagus. By what can be complicated this pathology?
A. Gastric dyspepsia
B. Esophageal cancer
C. Gastric ulcer
D. Erosive gastritis
E. Duodenal ulcer
8. A 55-year-old patient complains on heartburn, which is exacerbated by bending forward, chest pain when swallowing. X-ray investigation revealed a hernia of the esophageal lumen of the diaphragm. GERD was established during fibrogastroscopy. Concomitant pathology - hypertension, constantly taking amlodipine. Direction of treatment?
A. Prescribe pantoprozole
B. Prescribe domperidone
C. Replace amlodipine with another antihypertensive
D. All of the abovementioned
E. None of the abovementioned
9. A patient complains of retrosternal pain, difficult swallowing, over 10 kg weight loss within three months, general weakness. In blood: hypochromic anaemia, neutrophilic leukocytosis. In feces: weakly positive Gregersen's reaction. On esophagram a filling defect with ill-defined serrated edges shows up along a large portion of the oesophagus. What is the most likely diagnosis?
A Sideropenic dysphagia
B Benign tumour
C Esophageal achalasia
D Peptic ulcer
E Esophageal carcinoma
10. A patient suffering from gastroesophageal reflux has taken from time to time a certain drug that "reduces acidity" over 5 years. This drug was recommended by a pharmaceutist. The following side effects are observed: osteoporosis, muscle asthenia, indisposition. What drug has such following effects?
A Aluminium-bearing antacid
B Inhibitor of proton pump
C H2-blocker
D Metoclopramide
E Gastrozepin

Practical lesson #19

Theme: Gastric dyspepsia. Chronic gastritis.

2. Goal:
To study:
- definition, etiology, pathogenesis, classification, clinical manifestations of gastric dyspepsia and chronic gastritis;
- diagnostics and differential diagnostics of functional dyspepsia and gastritis;
- strategies of patients management with gastric dyspepsia;
- schemes of Helicobacter pylori eradication therapy and treatment of other typer of gastritis.

Basic concepts. Definition of dyspepsia. Aetiology. Red flag symptoms. Diagnosis and differential diagnosis. Gastritis: definition, epidemiology, aetiology. Pathophysiology. Classification of gastritis. Diagnostic and differential diagnostics. Treatment.

Dyspepsia is defined as chronic or recurrent pain or discomfort centered in the upper abdomen. Discomfort is defined as a subjective negative feeling that is nonpainful, and can incorporate a variety of symptoms including early satiety or upper abdominal fullness. Patients presenting with predominant or frequent (more than once a week) heartburn or acid regurgitation should be considered to have gastroesophageal reflux disease (GERD) until proven otherwise.

Evaluation

History:

History of present illness should elicit a clear description of the symptoms, including whether they are acute or chronic and recurrent. Other elements include timing and frequency of recurrence, any difficulty swallowing, and relationship of symptoms to eating or taking drugs. Factors that worsen symptoms (particularly exertion, certain foods, or alcohol) or relieve them (particularly eating or taking antacids) are noted.

Review of systems seeks concomitant GI symptoms such as anorexia, nausea, vomiting, hematemesis, weight loss, and bloody or black (melanotic) stools. Other symptoms include dyspnea and diaphoresis.

Past medical history should include known GI and cardiac diagnoses, cardiac risk factors (eg, hypertension, hypercholesterolemia), and the results of previous tests that have been done and treatments that have been tried. Drug history should include prescription and illicit drug use as well as alcohol.

Physical examination:

Review of vital signs should note presence of tachycardia or irregular pulse.

General examination should note presence of pallor or diaphoresis, cachexia, or jaundice. Abdomen is palpated for tenderness, masses, and organomegaly. Rectal examination is done to detect gross or occult blood.

Red flags:

The following findings are of particular concern:

- ✓ Acute episode with dyspnea, diaphoresis, or tachycardia
- ✓ Anorexia
- ✓ Nausea or vomiting
- ✓ Weight loss
- ✓ Blood in the stool
- ✓ Dysphagia or odynophagia
- ✓ Failure to respond to therapy with H_2 blockers or proton pump inhibitors (PPIs)

Dyspeptic patients more than 55 yr old, or those with alarm features (bleeding, anemia, early satiety, unexplained weight loss (>10% body weight), progressive dysphagia, odynophagia, persistent vomiting, a family history of gastrointestinal cancer, previous esophagogastric

malignancy, previous documented peptic ulcer, lymphadenopathy, or an abdominal mass) should undergo prompt endoscopy to rule out peptic ulcer disease, esophagogastric malignancy, and other rare upper gastrointestinal tract disease.

In patients aged 55 yr or younger with no alarm features, the clinician may consider two approximately equivalent management options: (i) test and treat for H. pylori using a validated noninvasive test and a trial of acid suppression if eradication is successful but symptoms do not resolve or (ii) an empiric trial of acid suppression with a proton pump inhibitor (PPI) for 4–8 wk. The test-and-treat option is preferable in populations with a moderate to high prevalence of H. pylori infection (>=10%), whereas the empirical PPI strategy is preferable in low prevalence situations.

Treatment

Specific conditions are treated. Patients without identifiable conditions are observed over time and reassured. Symptoms are treated with PPIs, H_2 blockers, or a cytoprotective agent. Prokinetic drugs (eg, metoclopramide, erythromycin) given as a liquid suspension also may be tried in patients with dysmotility-like dyspepsia. However, there is no clear evidence that matching the drug class to the specific symptoms (eg, reflux vs dysmotility) makes a difference. Misoprostoland anticholinergics are not effective in functional dyspepsia. Drugs that alter sensory perception (eg, tricyclic antidepressants) may be helpful.

Key Points

- ✓ Coronary ischemia is possible in a patient with acute “gas.”
- ✓ Endoscopy is indicated for patients > 45 or with red flag findings.
- ✓ Empiric treatment with an acid blocker is reasonable for patients < 45 without red flag findings; patients who do not respond in 2 to 4 wk require further evaluation.

Gastritis is inflammation of the gastric mucosa caused by any of several conditions, including infection (Helicobacter pylori), drugs (NSAIDs, alcohol), stress, and autoimmune phenomena (atrophic gastritis). Many cases are asymptomatic, but dyspepsia and GI bleeding sometimes occur. Diagnosis is by endoscopy. Treatment is directed at the cause but often includes acid suppression and, for H. pyloriinfection, antibiotics.

Gastritis is classified as erosive or nonerosive based on the severity of mucosal injury. It is also classified according to the site of involvement (ie, cardia, body, antrum). Gastritis can be further classified histologically as acute or chronic based on the inflammatory cell type. No classification scheme matches perfectly with the pathophysiology; a large degree of overlap exists. Some forms of gastritis involve acid-peptic and H. pylori disease. Additionally, the term is often loosely applied to nonspecific (and often undiagnosed) abdominal discomfort and gastroenteritis.

Acute gastritis is characterized by PMN infiltration of the mucosa of the antrum and body.

Chronic gastritis implies some degree of atrophy (with loss of function of the mucosa) or metaplasia. It predominantly involves the antrum (with subsequent loss of G cells and decreased gastrin secretion) or the corpus (with loss of oxyntic glands, leading to reduced acid, pepsin, and intrinsic factor).

EROSIVE GASTRITIS

Erosive gastritis is gastric mucosal erosion caused by damage to mucosal defenses. It is typically acute, manifesting with bleeding, but may be subacute or chronic with few or no symptoms. Diagnosis is by endoscopy. Treatment is supportive, with removal of the inciting cause. Certain ICU patients (eg, ventilator-bound, head trauma, burn, multisystem trauma) benefit from prophylaxis with acid suppressants.

Causes of erosive gastritis include NSAIDs, alcohol, stress, and less commonly radiation, viral infection (eg, cytomegalovirus), vascular injury, and direct trauma (eg, nasogastric tubes).

Superficial erosions and punctate mucosal lesions occur. These may develop as soon as 12 h after the initial insult. Deep erosions, ulcers, and sometimes perforation may occur in severe or untreated cases. Lesions typically occur in the body, but the antrum may also be involved.

Acute stress gastritis, a form of erosive gastritis, occurs in about 5% of critically ill patients. The incidence increases with duration of ICU stay and length of time the patient is not receiving enteral feeding. Pathogenesis likely involves hypoperfusion of the GI mucosa, resulting in impaired mucosal defenses. Patients with head injury or burns may also have increased secretion of acid.

Symptoms and Signs

Patients with mild erosive gastritis are often asymptomatic, although some complain of dyspepsia, nausea, or vomiting. Often, the first sign is hematemesis, melena, or blood in the nasogastric aspirate, usually within 2 to 5 days of the inciting event. Bleeding is usually mild to moderate, although it can be massive if deep ulceration is present, particularly in acute stress gastritis. Acute and chronic erosive gastritis are diagnosed endoscopically.

Diagnosis

Acute and chronic erosive gastritis are diagnosed endoscopically.

Treatment

- ✓ For bleeding: Endoscopic hemostasis
- ✓ For acid suppression: A proton pump inhibitor or H_2 blocker

In severe gastritis, bleeding is managed with IV fluids and blood transfusion as needed. Endoscopic hemostasis should be attempted, with surgery (total gastrectomy) a fallback procedure. Angiography is unlikely to stop severe gastric bleeding because of the many collateral vessels supplying the stomach. Acid suppression should be started if the patient is not already receiving it.

For milder gastritis, removing the offending agent and using drugs to reduce gastric acidity may be all that is required.

Prevention

Prophylaxis with acid-suppressive drugs can reduce the incidence of acute stress gastritis. However, it mainly benefits certain high-risk ICU patients, including those with severe burns, CNS trauma, coagulopathy, sepsis, shock, multiple trauma, mechanical ventilation for > 48 h, hepatic or renal failure, multiorgan dysfunction, and history of peptic ulcer or GI bleeding.

Prophylaxis consists of IV H_2 blockers, proton pump inhibitors, or oral antacids to raise intragastric pH> 4.0. Repeated pH measurement and titration of therapy are not required. Early enteral feeding also can decrease the incidence of bleeding.

Acid suppression is not recommended for patients simply taking NSAIDs unless they have previously had an ulcer.

NONEROSIVE GASTRITIS

Nonerosive gastritis refers to a variety of histologic abnormalities that are mainly the result of H. pyloriinfection. Most patients are asymptomatic. Diagnosis is by endoscopy. Treatment is eradication of H. pylori and sometimes acid suppression.

Pathology

Superficial gastritis:

Lymphocytes and plasma cells mixed with neutrophils are the predominant infiltrating inflammatory cells. Inflammation is superficial and may involve the antrum, body, or both. It is usually not accompanied by atrophy or metaplasia. Prevalence increases with age.

Deep gastritis:

Deep gastritis is more likely to be symptomatic (eg, vague dyspepsia). Mononuclear cells and neutrophils infiltrate the entire mucosa to the level of the muscularis, but exudate or crypt abscesses seldom result, as might be expected by such infiltration. Distribution may be patchy. Superficial gastritis may be present, as may partial gland atrophy and metaplasia.

Gastric atrophy:

Atrophy of gastric glands may follow in gastritis, most often long-standing antral (sometimes referred to as type B) gastritis. Some patients with gastric atrophy have autoantibodies to parietal cells, usually in association with corpus (type A) gastritis and pernicious anemia.

Atrophy may occur without specific symptoms. Endoscopically, the mucosa may appear normal until atrophy is advanced, when submucosal vascularity may be visible. As atrophy becomes

complete, secretion of acid and pepsin diminishes and intrinsic factor may be lost, resulting in vitamin B_{12}malabsorption.

Metaplasia:

Two types of metaplasia are common in chronic nonerosive gastritis: mucous gland and intestinal.

Mucous gland metaplasia (pseudopyloric metaplasia) occurs in the setting of severe atrophy of the gastric glands, which are progressively replaced by mucous glands (antral mucosa), especially along the lesser curve. Gastric ulcers may be present (typically at the junction of antral and corpus mucosa), but whether they are the cause or consequence of these metaplastic changes is not clear.

Intestinal metaplasia typically begins in the antrum in response to chronic mucosal injury and may extend to the body. Gastric mucosa cells change to resemble intestinal mucosa—with goblet cells, endocrine (enterochromaffin or enterochromaffin-like) cells, and rudimentary villi—and may even assume functional (absorptive) characteristics. Intestinal metaplasia is classified histologically as complete (most common) or incomplete. With complete metaplasia, gastric mucosa is completely transformed into small-bowel mucosa, both histologically and functionally, with the ability to absorb nutrients and secrete peptides. In incomplete metaplasia, the epithelium assumes a histologic appearance closer to that of the large intestine and frequently exhibits dysplasia. Intestinal metaplasia may lead to stomach cancer.

Symptoms and Signs

Most patients with H. pylori–associated gastritis are asymptomatic, although some have mild dyspepsia or other vague symptoms. Often the condition is discovered during endoscopy performed for other purposes. Testing of asymptomatic patients is not indicated. Once gastritis is identified, testing for H. pylori is appropriate.

Diagnosis

- Endoscopy

Often, the condition is discovered during endoscopy done for other purposes. Testing of asymptomatic patients is not indicated. Once gastritis is identified, testing for H. pylori is appropriate.

Treatment

- ✓ Eradication of H. pylori
- ✓ Sometimes acid-suppressive drugs

Treatment of chronic nonerosive gastritis is H. pylori eradication. Treatment of asymptomatic patients is somewhat controversial given the high prevalence of H. pylori–associated superficial gastritis and the relatively low incidence of clinical sequelae (ie, peptic ulcer disease). However, H. pylori is a class J carcinogen; eradication removes the cancer risk. In H. pylori–negative patients, treatment is directed at symptoms using acid-suppressive drugs (eg, H_2 blockers, proton pump inhibitors) or antacids.

POSTGASTRECTOMY GASTRITIS

Postgastrectomy gastritis is gastric atrophy developing after partial or subtotal gastrectomy (except in cases of gastrinoma).

Metaplasia of the remaining corpus mucosa is common. The degree of gastritis is usually greatest at the lines of anastomosis.

Several mechanisms are responsible: bile reflux, which is common after such surgery, damages the gastric mucosa; loss of antral gastrin decreases stimulation of parietal and peptic cells, causing atrophy; and vagotomy may result in a loss of vagal trophic action.

There are no specific symptoms of gastritis. Postgastrectomy gastritis often progresses to severe atrophy and achlorhydria. Production of intrinsic factor may cease with resultant vitamin B_{12} deficiency (which may be worsened by bacterial overgrowth in the afferent loop). The relative risk of gastric adenocarcinoma seems to increase 15 to 20 yr after partial gastrectomy; however, given the low absolute incidence of postgastrectomy cancer, routine endoscopic surveillance is probably not cost effective, but upper GI symptoms or anemia in such patients should prompt endoscopy.

UNCOMMON GASTRITIS SYNDROMES

Ménétrier's disease:

This rare idiopathic disorder affects adults aged 30 to 60 and is more common among men. It manifests as a significant thickening of the gastric folds of the gastric body but not the antrum. Gland atrophy and marked foveolar pit hyperplasia occur, often accompanied by mucous gland metaplasia and increased mucosal thickness with little inflammation. Hypoalbuminemia (the most consistent laboratory abnormality) caused by GI protein loss may be present (protein-losing gastropathy). As the disease progresses, the secretion of acid and pepsin decreases, causing hypochlorhydria.

Symptoms are nonspecific and commonly include epigastric pain, nausea, weight loss, edema, and diarrhea. Differential diagnosis includes (1) lymphoma, in which multiple gastric ulcers may occur; (2) mucosa-associated lymphoid tissue (MALT) lymphoma, with extensive infiltration of monoclonal B lymphocytes; (3) Zollinger-Ellison syndrome with associated gastric fold hypertrophy; and (4) Cronkhite-Canada syndrome, a mucosal polypoid protein-losing syndrome associated with diarrhea. Diagnosis is made by endoscopy with deep mucosal biopsy or full-thickness laparoscopic gastric biopsy.

Various treatments have been used, including anticholinergics, antisecretory drugs, and corticosteroids, but none have proved fully effective. Partial or complete gastric resection may be necessary in cases of severe hypoalbuminemia.

Eosinophilic gastritis:

Extensive infiltration of the mucosa, submucosa, and muscle layers with eosinophils often occurs in the antrum. It is usually idiopathic but may result from nematode infestation. Symptoms include nausea, vomiting, and early satiety. Diagnosis is by endoscopic biopsy of involved areas. Corticosteroids can be successful in idiopathic cases; however, if pyloric obstruction develops, surgery may be required.

Mucosa-associated lymphoid tissue (MALT) lymphoma:

This rare condition is characterized by massive lymphoid infiltration of the gastric mucosa, which can resemble Ménétrier's disease.

Gastritis caused by systemic disorders:

Sarcoidosis, TB, amyloidosis, and other granulomatous diseases can cause gastritis, which is seldom of primary importance.

Gastritis caused by physical agents:

Radiation and ingestion of corrosives (especially acidic compounds) can cause gastritis. Exposure to > 16 Gy of radiation causes marked deep gastritis, usually involving the antrum more than the corpus. Pyloric stenosis and perforation are possible complications of radiation-induced gastritis.

Infectious (septic) gastritis:

Except for H. pylori infection, bacterial invasion of the stomach is rare and mainly occurs after ischemia, ingestion of corrosives, or exposure to radiation. On x-ray, gas outlines the mucosa. The condition can manifest as an acute surgical abdomen and has a very high mortality rate. Surgery is often necessary.

Debilitated or immunocompromised patients may develop viral or fungal gastritis with cytomegalovirus,Candida, histoplasmosis, or mucormycosis; these diagnoses should be considered in patients with exudative gastritis, esophagitis, or duodenitis.

Equipment: study room, acknowledge with protocol and procedure of fibrogastroduodenoscopy and X-ray with contrast after barium swallowing during visit to functional department (1st floor in University Clinic). Results of these investigations are provided to students during lesson.

Learning hours: 2 hours.

Plan of the lesson

I. Organizational moment (greetings, checking who is present on the lesson, announcing topic and goal of the lesson, motivating applicants to study the topic).

II. Control of basic knowledge (oral questioning, tests, checking of how clinical cases and workbooks are fulfilled).

2.1. Demands for applicants theoretical preparation

Applicant should know.

Didactic units list:

- The difference between the concepts of diagnosis and symptoms of dyspepsia.
- Components of red flags and "small signs" of stomach cancer .
- Definition, classification, etiology and pathogenesis of organic and functional dyspepsia.
- Strategies for patient management with the syndrome of stomach dyspepsia.
- Definition, etiology, pathogenesis, classification, clinic, diagnosis and treatment of gastritis.
- Indication to eradication of H.Pilory and schemes of eradication therapy.

Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Tests for self-control

1. The"symptoms of anxiety" include:
A. Unmotivated weight loss.
B. Feeling of weakness and anxiety. +
C. Unmotivated iron deficiency anemia.
D. Family history of gastric cancer.
E. Lymphadenopathy.
2. Organic dyspepsia is:
A. Peptic duodenal ulcer.
B. Stomach cancer.
C. Postprandial distress syndrome. +
D. Erosive duodenopaty.
E. Cholelithiasis.
3. Male, 20 years, complaints: squeezing epigastric pain, heartburn, belching sour. Objective: a satisfactory condition. On palpation pain in the epigastric region.Fibrogastroduodenoscopy with the morphology of biopsy specimens revealed no pathology. What drug is most effective?
A. Omeprazole. +
B. Almagel.
C. De-nol.
D. Gastrotsepin.
E. Metoclopramide.
4. Male 67 years old, the complaint of loss of appetite, tightness in the epigastrium after meals, belching air, nausea. In the study of gastric secretion revealed ahily.Fibrogastroduodenoscopy - gastric mucosa thinned, atrophic. Your diagnosis?
A. Gastritis A. +
B. Stomach cancer.
C. Chronic diskinetic colitis.
D. Chronic gastroduodenitis.
E. Gastritis with intestinal metaplasia
5. Patient 35y.o., abuse alcohol. Complaints: epigastric pain alternation 1-1.5 hours after meal.Fibrogastroduodenoscopy - in the stomach antrum expressed hyperemia, increased vulnerability of the mucosa. The most common cause of revealed pathology?
A. H. Pilory infection.

B. Presence of antibody to parietal cells.
C. Alimentary factor.
D. Toxic effect of alcohol.
E. Stress.
6. Patient 55 years, complaints: aching epigastric pain, nausea and heartburn. These complaints appeared after treatment with indomethacin. Objective: abdomen is soft, pain in epigastric region. Liver and spleen are not enlarged. What should do first?
A. Cancel indomethacin. +
B. Prescribe a hunger for 2 days.
C. Wash out the stomach.
D. Prescribe antacids.
E. Prescribe drugs, acting on H. Pilory.
7. Patient was diagnosed Chronic hypoacidic gastritis and moderate anemia. Chronic fundal gastritis type A was suspected. Chose the mechanism of development this gastritis:
A. Autoimmune gastritis type A. +
B. Chronic gastritis type B.
C. Chronic gastritis type C.
D. Chronic gastritis, pangastritis.
E. chronic gastroduodenitis, exacerbation.
8. Patient suffers from gastritis. For last 6 month complaints with epigastral pain, nausea, lack of appetite, weight loss, aversion to meat. Objective: low nutrition, above the left clavicle palpable lymph node.Which disease should be excluded first?
A. Stomach cancer. +
B. Cancer of pancreas.
C. Stomach ulcer disease.
D. Chronic gastritis.
E. Cancer of gall bladder.
9. The patient complains on epigastric pain, nausea, weakness, vomiting, feeling of fullness in the stomach. From history: last night was in a cafe. Objective: pale skin, tongue coated with gray patina, salivation. During palpation - epigastric pain. Ps 100 bpm, BP 110/60 mmHg. Primary diagnosis?
A. Acute gastitis. +
B. Duodenum ulcer disease.
C. Stomach ulcer disease.
D. Chronic gastritis.
E. Acute pancreatitis.
10. Patient 52 y.o., for 10 years suffers from autoimmune gastritis A. During planned examination complaints on periodic nausea, heaviness in epigastric region after meal. Last exacerbation – 6 month ago. Follow-up the diet, smokes 10 cigarettes per day. What methods of gastric cancer prevention are needed in this case?
A. Stop smoking. +
B. Periodical antacids intake.
C. Periodical anti H.Pilory drugs intake.
D. Periodical Gastrotsepin intake.
E. Periodical H_2-hystamine blockers intake.

III. Formation of professional skills, abilities:
3.1. content of tasks (tasks, clinical situations, etc.)
Case history #1 A 42-year-old man presents with a recent history of abdominal pain, distension, and nausea. Urea breath testing for Helicobacter pylori is positive.
Case history #2 A 58-year-old white woman of North European descent presents with a 2-month history of increasing fatigue, difficulty with ambulation, and memory deficits. Family history is

notable for autoimmune disease. Laboratory findings are remarkable for a macrocytic anaemia, a markedly reduced serum vitamin B_{12}, and presence of anti-parietal cell antibodies.

Task: Applicant should write diagnosis, plan of investigation, carry out differential diagnosis, prescribe treatment for both case histories.

3.2. recommendations (instructions) for performing tasks (professional algorithms, orientation maps for the formation of practical skills, etc.)

Professional algorithms.

IV. Patient's examination.

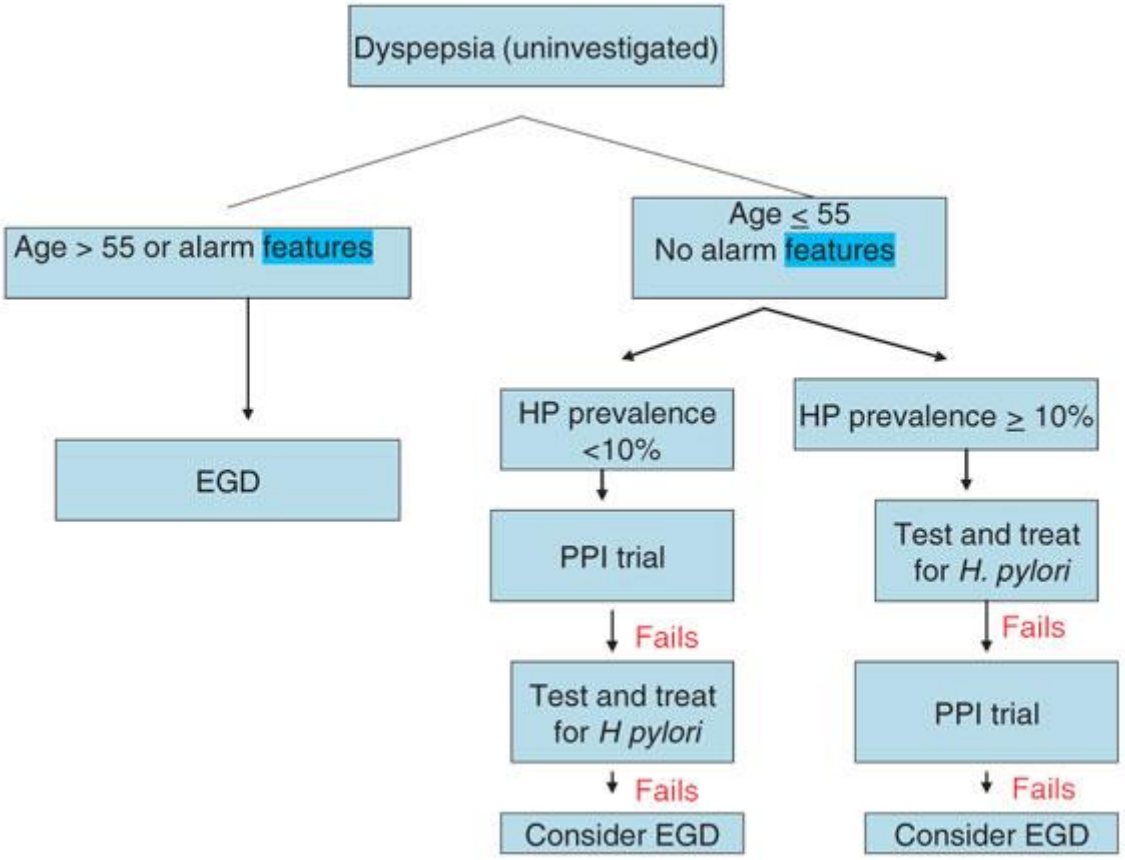
During patient's examination students should keep such communicative skills:

1. Friendly face expression.
2. Kind voice tone.
3. Greetings, showing concern and respect about the patient.
4. Find out patient's complaints and anamnesis .
5. Explanation of investigation results.
6. Explanation of specific actions (hospitalization, carrying out investigations) which are planned to be performed in the future.
7. Finishing of the talk.

V. Patient's examination and investigation algorithm.

1. Student should perform palpation of epigastria area and make percussion for defining of lower border of stomach's great curvature.
2. It should be explained to patient which investigation will be held and indications for this investigation.
3. A doctor should receive patient's agreement on investigation.
4. A doctor should warn patient about possibilities of unpleasant feelings during oesophagogastroduodenoscopy.
5. Results of investigation should be explained to a patient.
6. Upper gastrointestinal (UGI) radiography is not recommended as an initial investigation for patients presenting with uninvestigated dyspepsia.
7. Endoscopic examination should be considered for older patients (>60 years old) with new onset (within a few months) of progressively worsening symptoms, particularly if alarm features (vomiting, bleeding, abdominal mass loss, dysphagia) are present.
8. Abdominal ultrasound is not recommended as a routine investigation for patients presenting with uninvestigated dyspepsia.
9. A therapeutic trial of PPI for 1-2 months can be used to predict response to treatment for uninvestigated dyspepsia. Symptom resolution at 1-2 months means a positive trial, and continuation of symptoms at 1-2 months means a negative trial.

Algorithm for the management of uninvestigateddyspepsia



1. Endoscopy should be done for patients 60 years of age or older presenting with dyspepsia, and only on a case-by-case basis in younger patients with alarm features.
2. Any patient with a family history of GI cancer, previous oesophago-gastric malignancy, lymphadenopathy, or abdominal mass should undergo EGD.
3. patients with uninvestigated dyspepsia aged below 60 years old without alarm feature air upper GI malignancy should undergo non-invasive testing for Hp-infection.
4. Both the urea breath test and the faecal antigen test are highly sensitive and specific assays for active H pylori infection.
5. If autoimmune gastritis is suspected, serum vitamin B_{12} and autoantibody studies should be ordered.
6. Patients with confirmed pernicious anaemia should undergo endoscopy to evaluate for any associated gastric malignancy.

VI. Step-by-step algorithm of treatment.

1. A patient should informed be about necessity of the prescribed treatment.
2. Dosages, drugs intake regimens, duration of treatment, side effects of the prescribed therapy should be kindly explained to patient.
3. A therapeutic trial of PPI for 1-2 months can be used to predict response to treatment for uninvestigated dyspepsia.
4. First-line treatment options include triple therapy (a proton-pump inhibitor plus clarithromycin, and amoxicillin) or quadruple therapy (a PPI plus bismuth plus tetracycline and metronidazole) is given for 14 days
5. For erosive gastritis symptomatic therapy with either H_2 antagonists or a PPI is effective and is essential when NSAID use has to be continued.

6. Patients with low serum vitamin B_{12} should be treated with intramuscular cyanocobalamin (vitamin B_{12}) for repletion.
7. For patients with primary bile reflux, or reflux following gastric or biliary surgery, symptomatic therapy with rabeprazole or sucralfate as an initial therapy is preferred to surgical intervention.

3.3. requirements for students work results.

As a results of studying students must perform the following:
-possess skills of communication and clinical examination of a patient with dyspepsia and gastritis;
-collect data on patient complaints, medical history, life history;
-evaluate information about the diagnosis of dyspepsia and gastritis using a standard procedure, based on the results of laboratory and instrumental studies. Determine the list of required clinical, laboratory and instrumental studies and evaluate their results;
- identify the leading clinical symptom or syndrome. Establish the most probable or syndrom diagnosis. Assign laboratory and instrumental investigations for patient. Carry out differential diagnosis of dyspepsia and gastritis. Establish preliminary and clinical diagnosis;
- determine the principles of treatment, the required regime of work/rest and alimentary regime of patients with dyspepsia and gastritis;
- diagnose emergencies in the clinic of gastritis;
- define tactics and provide emergency medical care;
- perform an expertise of work capacity of patients with dyspepsia and gastritis.

3.4. control materials for the final stage of the lesson.

Work 1
1. Collection of complaints, anamnesis, examination of a patient with gastric dyspepsia and chronic gastritis.
2. Detection of clinical and instrumental symptoms.
3. Grouping symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data (clinical analysis of blood, urine, biochemical analysis of blood, PPI - test, radiography of the esophagus and stomach with barium, FGDS, ECG, echocardiography, etc.).
6. Carrying out a differential diagnosis.
7. Formulation of the clinical diagnosis.
8. Write a prescription list for patients diagnosed with gastric dyspepsia and chronic gastritia, which would include diet and prescribed drugs.
9. Determining of the disability degree.

Work 2.
Assignment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.
Work in the Internet, in the reading room of the department library with thematic literature.
The student fills in the protocol of the patient's examination. An example of the initial examination of the patient is attached.
The tests for self-control with standard answers.
1. Gastric juice analysis of a 42-year-old male patient revealed absence of free hydrochloric acid at all stages. Endoscopy revealed pallor, thinning of gastric mucosa, smoothed folds. Microscopically the atrophy of glands with intestinal metaplasia was found. What disease is this situation typical for?

A Chronic type A gastritis
B Chronic type B gastritis
C Chronic type C gastritis
D Menetrier disease
EStomach cancer

2. A 23-year-old patient complains of a dull ache, sensation of heaviness and distension in the epigastrium immediately after meals, foul-smelling eructation; dry mouth, empty stomach nausea, diarrhoea. Objectively: the skin is pale, the patient is of thin build. Abdomen is soft on palpation, there is epigastric pain. The liver does not extend beyond the costal arch. In blood: Hb - 110 g/l, RBCs - $3,4x10^{12}$/l, WBC count is normal. ESR - 16 mm/h. What is the most informative study that will allow make a diagnosis?
A X-ray of digestion organs
B Esophageal gastroduodenoscopy
C Study of gastric juice
D pH-metry
E Duodenal probing

3. A 27 year old man complains of pains in epigastrium which are relieved by food intake. EGDFS shows antral erosive gastritis, biopsy of antral mucous presents Helicobacter Pylori. Diagnosis is:
A Reflux-gastritis
B Gastritis of type A
C Gastritis of type B
D Menetrier's gastritis
E Rigid antral gastritis

4. A 50 year old patient has been admitted to the clinics with atrophic gastritis. Blood count: erythrocytes - $3,8*10^{12}$/l, Hb - 68 g/l, c.i. - 1, macroanisocytosis, poikilocytosis. There is megaloblastic type of haemopoesis. A number of leukocytes, reticulocytes and thrombocytes is reduced. Which pathology is suspected?
A Post-hemorrhagic anemia
B Irondeficiency anemia
C Hemolytic anemia
D B_{12}-deficiency anemia
E Thalassaemia

5. A 27 y.o. man complained of aching epigastric pain right after meal, heartburn and nausea. Stomach endoscopy revealed a large amount of mucus, hyperemia and edema of mucous membrane in gastric fundus with areas of atrophy. Make a diagnosis.
A Menetrier's disease
B Chronic gastritis of type B
C Peptic ulcer of stomach
D Chronic gastritis of type C
EChronic gastritis of type A

6. A 39 y.o. woman complaines of squeezed epigastric pain 1 hour after meal and heartburn. She had been ill for 2 years. On palpation, there was moderate tenderness in pyloroduodenal area. Antral gastritis was revealed on gastroscopy. What study can establish genesis of the disease?
A Revealing of Helicobacter infection in gastric mucosa
B Detection of autoantibodies in the serum
C Gastrin level in blood
D Examination of stomach secretion
E Examination of stomach motor function

7. A 32 year old patient complains about heartburn and dull pain in the epigastrium that appear 2-3 hours after meal. Exacerbations happen in spring and in autumn. The patient has food intolerance of eggs and fish. Objectively: stomach palpation reveals painfulness in the gastroduodenal area. Upper

endoscopy revealed a 5 mm ulcer on the anterior wall of duodenum. Urease test is positive. What is the most probable leading mechanism of disease development?
A Dietary allergy
B Helicobacterial infection
C Autoantibody production
D Reduced prostaglandin synthesis
E Disorder of gastric motor activity
8. A 42 y.o. man who has been ill with duodenal ulcer for 20 years complains of getting a sense of heaviness in stomach after meal, foul-smelling eructation, vomiting, weight loss. Objectively: his state is relatively satisfactory, tissue turgor is diminished. On palpation the abdomen is soft, there are no symptoms of peritoneal irritation, "splashing sounds" in epigastrium. Defecation - once in 3 days. What complication corresponds with the patient's state and described clinical presentations?
A Stomach cancer
B Concealed ulcer perforation
C Ulcerative pyloric stenosis
D Ulcer penetration
E Chronic pancreatitis
9. A 33 y.o. male patient was admitted to a hospital. A patient is pale, at an attempt to stand up he complains of strong dizziness. There was vomiting like coffee-grounds approximately hour ago. BP- 90/60 mm Hg., pulse- 120 b/min. In anamnesis, a patient has suffered from ulcer of the stomach, painless form during 4 years. An ulcer was exposed at gastrofiberoscopy. Your diagnosis:
A Acute pleurisy
B Ulcer of duodenum, complicated with bleeding
C Erosive gastritis
D Ulcer of stomach, complicated with bleeding
E Acute myocardial infarction, abdominal form
10. In autumn a 25-year-old patient developed stomach ache arising 1,5-2 hours after having mealsand at night. He complains of pyrosis and constipation. The pain is getting worse after consuming spicy, salty and sour food, it can be relieved by means of soda and hot-water bag. The patient has been suffering from this disease for a year. Objectively: furred moist tongue. Abdomen palpation reveals epigastrial pain on the right, resistance of abdominal muscles in the same region. What is the most likely diagnosis?
A Chronic pancreatitis
B Chronic cholecystitis
C Diaphragmatic hernia
D Stomach ulcer
E Duodenal ulcer
Standard answers: 1-A, 2-B,3-C, 4-D, 5-E, 6-A, 7-B, 8-C, 9-D, 10-E.

4. Summarizing, announcing the final grade, announcing the task for the next lesson.

Recommended resourses:
- Basic literature source:
1. Malfertheiner P, Megraud F, O'Morain C et al Management of Helicobacter pylori infection – the Maastricht V / Florence Consensus Report //Gut. – 2017. – Vol.66. – P. 6-30
2. Chey WD, Leontiadis GI, Howden CW, Moss SF. ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. Am J Gastroenterol. 2017;112(2):212-239.
3. Moayyedi PM, Lacy BE, Andrews CN et al. ACG and CAG Clinical Guideline: Management of Dyspepsia. Am J Gastroenterol. 2017;112(7):988-1013.
4. Pinto-Sanchez MI, Yuan Y, Bercik P, et al. Proton pump inhibitors for functional dyspepsia. Cochrane Database Syst Rev. 2017 Mar 8;(3):CD011194.

Appendix 1

Example of the primary examination of the patient

Passport data: name and surname, age

Complaints: *dull, gnawing ache in the epigastric region. Pain appears after eating fried and spice food, relieved by drinking milk and is helped partially by ranitidine.*

Anamnesis morbid

2-month history of intermittent upper abdominal pain. He had a similar but milder episode about 2 years ago, which was treated with omeprazole.

Anamnesis vitae

Living conditions are satisfactory. Botkin's disease, tuberculosis, sexually transmitted diseases, malaria denies.

Professional anamnesis: not burdened.

Hereditary history is not burdened.

Pave not been in contact with infectious patients for the last 3 days. He has not left the country in the last 3 years.

Hereditary history*: not burdened*

Neurological history

At the time of examination signs of focal neurological symptoms were not detected.

Allergic history*: not burdened*

Epidemiology

Tuberculosis, malaria, viral hepatitis, Botkin's disease, veneral disease, HIV, AIDS, pediculosis – denies.

Oncoanamnesis*: denies.*

Insurance anamnesis*: There is no need to issue a seak leave, for the last 12 months a seak leave document has not been issued in this regard.*

Postponed operations*: denies.*

Bad habits*: smokes for 10 years, 1 pack a day*

Examination of organ systems:

GENERAL Condition: satisfactory

CONSCIOUSNESS: clear

Body shape: hypostenic

Fatness: low nutrition

POSITION OF THE PATIENT: active

BODY TEMPERATURE: 36.6 C. Signs of alcohol intoxication - no

SKIN: Skin of normal color, clean. Tissue turgor is normal. Skin pigmentation: depigmentation - no. Rash: no; other changes in the skin: no.

Visible mucous membranes: Normal color

LYMPH NODES: not enlarged

THYROID GLAND: no pathology

Oncological examination was performed, no visual forms of oncopathology were detected

Cardiovascular system:

PERCUSSION OF THE HEART: the limits of relative cardiac dullness: right on the right edge of the sternum, upper -III rib on the left parasternalis line, left - 1 cm outward from the left mediaclavicularis line in the V intercostal space

HEART activity: rhythmic, heart rate - 74 per 1 min. Pulse 74 in 1 min. Heart tones: muffled

HEART MURMURS: no

EDEMA: no

BP 125 / 85 mm Hg

EXAMINATION OF ARTERIES: no pathology

VEIN STUDY: no pathology

RESPIRATORY SYSTEM:

BREATHING: no dyspnea at rest, RR 16 in 1 min.

Sputum: no
CHEST: cylindrical, not deformed. Intercostal spaces: NOT smoothed. Participation of additional muscles: no, RR – 16 in 1 min. SpO2 = 98%
Percussion over the lungs: clear lung sound.
PULMONARY AUSCULTATION: vesicular breathing over both lungs. Pleural friction noise - no
DIGESTIVE SYSTEM:
TONGUE: wet; covered with white plaque
Tonsils: not enlarged
STOMACH: participates in the act of breathing. No hernia. Pulsation in the epigastrium - no. There is no dilation of the subcutaneous veins
Palpation: moderately painful in the epigastric region
Pathological symptoms: not detected
Liver: not enlarged
Gallbladder: not palpable
Pancreas: painless
Spleen: not palpable,
PERCUTIONAL SOUND OVER THE ABDOMINAL CAVITY: unchanged,
FECES: normal, no pathological impurities
URINARY SYSTEM:
Palpation of the kidneys: not palpable
Pasternatsky's symptom is negative on both sides.
Urination: free, painless, frequency per day: 3-4 times.
Urinary incontinence: no.
SENSES:
SIGHT: not violated (OU). There is no other pathology
HEARING: normal, no deafness, pain: no. Tinnitus: no.
Musculoskeletal system:
Pathology of the musculoskeletal system was not detected
On the basis of complaints, anamnesis, objective examination, it is possible to make a preliminary diagnosis:
Chronic gastritis, exacerbation stage
Plan of investigation
general blood test, general urine test, glycemia level (8.00, 13.00, 17.00, 21.00)
Biochemistry: liver tests, glucose, transaminases, protein, lipid spectrum, coagulogram, amylase, AF, LDG, GGT, CPK, serum iron, potassium, CRP, seromucoid, RF, ASLO.
ECG, FGDS with biopsy, helpil-test, ultrasound of abdominal organs
Consultation with a gastroenterologist.
Treatment plan
Normalization of lifestyle
Diet
Drug therapy:
- Omeprazole 20 mg - 1 tab. x 2 times/day, 20 minutes before eating
- Eradication of Helicobacter pylori if there is a positive helpil test
Scheme of eradication:

i. *Omeprazole 20 mg x 2 times a day*
ii. *Amoxicillin 1000 mg x 2 times a day*
iii. *Clarithromycin 500 mg x 2 times a day for 10-14 days*

At inefficiency of three-component therapy:

iv. *Omeprazole 20 mg x 2 times a day*
v. *Bismuth subcitrate 120 mg x 4 times a day*
vi. *Metronidazole 500 mg x 3 times a day*
vii. Tetracycline 500 mg x 4 times a day for 10-14 days

Appendix 1

Tests of basic knowledge level in KROK format

Theme 19. Gastric dyspepsia. Chronic gastriris

1. A 39 y.o. woman complaines of squeezed epigastric pain 1 hour after meal and heartburn. She had been ill for 2 years. On palpation, there was moderate tenderness in pyloroduodenal area. Antral gastritis was revealed on gastroscopy. What study can establish genesis of the disease?
A . Revealing of Helicobacter infection in gastric mucosa
B. Detection of autoantibodies in the serum
C. Gastrin level in blood
D. Examination of stomach secretion
E. Examination of stomach motor function

2. A 32 year old patient complains about heartburn and dull pain in the epigastrium that appear 2-3 hours after meal. Exacerbations happen in spring and in autumn. The patient has food intolerance of eggs and fish. Objectively: stomach palpation reveals painfulness in the gastroduodenal area. Upper endoscopy revealed a 5 mm ulcer on the anterior wall of duodenum. Urease test is positive. What is the most probable leading mechanism of disease development?
A. Dietary allergy
B. Helicobacterial infection
C. Autoantibody production
D. Reduced prostaglandin synthesis
E. Disorder of gastric motor activity

3. A 42 y.o. man who has been ill with duodenal ulcer for 20 years complains of getting a sense of heaviness in stomach after meal, foul-smelling eructation, vomiting, weight loss. Objectively: his state is relatively satisfactory, tissue turgor is diminished. On palpation the abdomen is soft, there are no symptoms of peritoneal irritation, "splashing sounds" in epigastrium. Defecation - once in 3 days. What complication corresponds with the patient's state and described clinical presentations?
A. Stomach cancer
B.Concealed ulcer perforation
C.Ulcerative pyloric stenosis
D.Ulcer penetration
E.Chronic pancreatitis

4. A 33 y.o. male patient was admitted to a hospital. A patient is pale, at an attempt to stand up he complains of strong dizziness. There was vomiting like coffee-grounds approximately hour ago. BP- 90/60 mm Hg., pulse- 120 b/min. In anamnesis, a patient has suffered from ulcer of the stomach, painless form during 4 years. An ulcer was exposed at gastrofiberoscopy. Your diagnosis:
A. Acute pleurisy
B.Ulcer of duodenum, complicated with bleeding
C.Erosive gastritis
D.Ulcer of stomach, complicated with bleeding
E.Acute myocardial infarction, abdominal form

5. In autumn a 25-year-old patient developed stomach ache arising 1,5-2 hours after having mealsand at night. He complains of pyrosis and constipation. The pain is getting worse after consuming spicy, salty and sour food, it can be relieved by means of soda and hot-water bag. The patient has been suffering from this disease for a year. Objectively: furred moist tongue. Abdomen palpation reveals epigastrial pain on the right, resistance of abdominal muscles in the same region. What is the most likely diagnosis?
A. Chronic pancreatitis
B.Chronic cholecystitis
C.Diaphragmatic hernia
D.Stomach ulcer
E.Duodenal ulcer

6. Gastric juice analysis of a 42-year-old male patient revealed absence of free hydrochloric acid at all stages. Endoscopy revealed pallor, thinning of gastric mucosa, smoothed folds. Microscopically the atrophy of glands with intestinal metaplasia was found. What disease is this situation typical for?
A. Chronic type A gastritis
B.Chronic type B gastritis
C.Chronic type C gastritis
D. Menetrier disease
E. Stomach cancer
7. A 23-year-old patient complains of a dull ache, sensation of heaviness and distension in the epigastrium immediately after meals, foul-smelling eructation; dry mouth, empty stomach nausea, diarrhoea. Objectively: the skin is pale, the patient is of thin build. Abdomen is soft on palpation, there is epigastric pain. The liver does not extend beyond the costal arch. In blood: Hb - 110 g/l, RBCs - $3,4x10^{12}$/l, WBC count is normal. ESR - 16 mm/h. What is the most informative study that will allow make a diagnosis?
A. X-ray of digestion organs
B.Esophageal gastroduodenoscopy
C.Study of gastric juice
D.pH-metry
E.Duodenal probing
8. A 27 year old man complains of pains in epigastrium which are relieved by food intake. EGDFS shows antral erosive gastritis, biopsy of antral mucous presents Helicobacter Pylori. Diagnosis is:
A. Reflux-gastritis
B.Gastritis of type A
C.Gastritis of type B
D.Menetrier's gastritis
E.Rigid antral gastritis
9. A 50 year old patient has been admitted to the clinics with atrophic gastritis. Blood count: erythrocytes - $3,8*10^{12}$/l, Hb - 68 g/l, c.i. - 1, macroanisocytosis, poikilocytosis. There is megaloblastic type of haemopoesis. A number of leukocytes, reticulocytes and thrombocytes is reduced. Which pathology is suspected?
A. Post-hemorrhagic anemia
B.Irondeficiency anemia
C.Hemolytic anemia
D.B_{12}-deficiency anemia
E.Thalassaemia
10. A 27 y.o. man complained of aching epigastric pain right after meal, heartburn and nausea. Stomach endoscopy revealed a large amount of mucus, hyperemia and edema of mucous membrane in gastric fundus with areas of atrophy. Make a diagnosis.
A. Menetrier's disease
B.Chronic gastritis of type B
C.Peptic ulcer of stomach
D.Chronic gastritis of type C
E.Chronic gastritis of type A

Practical lesson #20

Theme: Ulcer disease and other peptic ulcers of stomach and duodenum.

Goal:
To study:
- etiology, pathogenesis of 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.P. 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. Ulcer disease: definition, epidemiology, aetiology. Pathophysiology. Classification. Risk factors. Diagnosis and differential diagnostics. Treatment. Complication. Emergency treatment.

A peptic ulcer is an erosion in a segment of the GI mucosa, typically in the stomach (gastric ulcer) or the first few centimeters of the duodenum (duodenal ulcer), that penetrates through the muscularis mucosae. Nearly all ulcers are caused by Helicobacter pylori infection or NSAID use. Symptoms typically include burning epigastric pain that is often relieved by food. Diagnosis is by endoscopy and testing for H. pylori. Treatment involves acid suppression, eradication of H. pylori (if present), and avoidance of NSAIDs.

Ulcers may range in size from several millimeters to several centimeters. Ulcers are delineated from erosions by the depth of penetration; erosions are more superficial and do not involve the muscularis mucosae. Ulcers can occur at any age, including infancy and childhood, but are most common among middle-aged adults.

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.

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.

Complications

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.

Surgery:

With current drug therapy, the number of patients requiring surgery has declined dramatically. Indications include perforation, obstruction, uncontrolled or recurrent bleeding, and, although rare, symptoms that do not respond to drug therapy.

Surgery consists of a procedure to reduce acid secretion, often combined with a procedure to ensure gastric drainage. The recommended operation for duodenal ulcer is highly selective, or parietal cell, vagotomy (which is limited to nerves at the gastric body and spares antral innervation, thereby obviating the need for a drainage procedure). This procedure has a very low mortality rate and avoids the morbidity associated with resection and traditional vagotomy. Other acid-reducing surgical procedures include antrectomy, hemigastrectomy, partial gastrectomy, and subtotal gastrectomy (ie, resection of 30 to 90% of the distal stomach). These are typically combined with truncal vagotomy. Patients who undergo a resective procedure or who have an obstruction require gastric drainage via a gastroduodenostomy (Billroth I) or gastrojejunostomy (Billroth II).

The incidence and type of postsurgical symptoms vary with the type of operation. After resective surgery, up to 30% of patients have significant symptoms, including weight loss, maldigestion, anemia, dumping syndrome, reactive hypoglycemia, bilious vomiting, mechanical problems, and ulcer recurrence.

Weight loss is common after subtotal gastrectomy; the patient may limit food intake because of early satiety (because the residual gastric pouch is small) or to prevent dumping syndrome and other postprandial syndromes. With a small gastric pouch, distention or discomfort may occur after a meal of even moderate size; patients should be encouraged to eat smaller and more frequent meals.

Maldigestion and steatorrhea caused by pancreaticobiliary bypass, especially with Billroth II anastomosis, may contribute to weight loss.

Anemia is common (usually from iron deficiency, but occasionally from vitamin B_{12} deficiency caused by loss of intrinsic factor or bacterial overgrowth) in the afferent limb, and osteomalacia may occur. IM vitamin B_{12} supplementation is recommended for all patients with total gastrectomy but may also be given to patients with subtotal gastrectomy if deficiency is suspected.

Dumping syndrome may follow gastric surgical procedures, particularly resections. Weakness, dizziness, sweating, nausea, vomiting, and palpitation occur soon after eating, especially hyperosmolar foods. This phenomenon is referred to as early dumping, the cause of which remains unclear but likely involves autonomic reflexes, intravascular volume contraction, and release of vasoactive peptides from the small intestine. Dietary modifications, with smaller, more frequent meals and decreased carbohydrate intake, usually help.

Reactive hypoglycemia or **late dumping** (another form of the syndrome) results from rapid emptying of carbohydrates from the gastric pouch. Early high peaks in blood glucose stimulate excess release of insulin, which leads to symptomatic hypoglycemia several hours after the meal. A high-protein, low-carbohydrate diet and adequate caloric intake (in frequent small feedings) are recommended.

Mechanical problems (including gastroparesis and bezoar formation) may occur secondary to a decrease in phase III gastric motor contractions, which are altered after antrectomy and vagotomy. Diarrhea is especially common after vagotomy, even without a resection (pyloroplasty).

Ulcer recurrence, according to older studies, occurs in 5 to 12% after highly selective vagotomy and in 2 to 5% after resective surgery. Recurrent ulcers are diagnosed by endoscopy and generally respond to either proton pump inhibitors or H_2 blockers. For ulcers that continue to recur, the completeness of vagotomy should be tested by gastric analysis, H. pylori should be eliminated if present, and Zollinger-Ellison syndrome should be ruled out by serum gastrin studies.

Equipment: study room, acknowledge with protocol and procedure of fibrogastroduodenoscopy and X-ray with contrast after barium swallowing during visit to functional department (1^{st} floor in University Clinic). Results of these investigations are provided to applicants during lesson.

Learning hours: 2 hours.

Plan of the lesson

I. Organizational moment (greetings, checking who is present on the lesson, announcing topic and goal of the lesson, motivating applicants to study the topic).

II. Control of basic knowledge (oral questioning, tests, checking of how clinical cases and workbooks are fulfilled).

2.1. Demands for applicants theoretical preparation

Applicants should know.

Didactic units list:

1. Definition. Etiology, pathogenesis of peptic ulcer.
2. Role of H.pylori, acidic-peptic factor and medications in occurrence of peptic ulcers and their relapses.
3. Features of flow of pH-positive and pH-negative ulcers.
4. Complications (perforation, penetration, bleeding, stenosis, malignancy).
5. Value of laboratory and instrumental methods of researches.
6. Methods of diagnostics of Hp-infection.
7. Differential diagnostics.
8. Modern tactic of ulcer treatment. Hp eradication therapy. Control of eradication.
9. Medicamental therapy of Hp-negative ulcers.
10. Indications to surgical treatment.
11. Primary and secondary prophylaxis.
12. Prognosis for life, convalescence and work capacity.

Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Tests for self-control

1. Male 27 years turned to the doctor due to exacerbation of peptic ulcer disease. During gastroscopy test for the presence of abnormal flora is taken. More likely to be found:

A. Helicobacter.+
B. Staphylococcus.
C. Candida.
D. Chlamydia.
E. Giardia.

2. Patient 42 y.o., suffers from duodenal ulcer disease for 20 years. Complaints: constant heaviness in stomach after meal, rancid belching, vomiting with eaten before meals, weight loss. Objective: tissue turgor reduced. Abdomen soft, no symptoms of irritation of the peritoneum, the sound of "splash" in the epigastrium. Defecation 1 time per 3 days. What complication of ulcer disease occurred?

A. Covered ulcer perforation.
B. Stomach cancer.
C. Ulcerative stenosis of the output of the stomach. +
D. Ulcer penetration.
E. Chronic pancreatitis

3. Male, 24 years, complaints: epigastric pain after 1-1,5 hours after meal and at night, frequent vomiting with relief. Sever smoker. Objective: during palpation muscles defence, pain in the right above novel. In stool – reaction for occult blood is positive. What is most likely diagnosis?

A. Chronic cholecystitis.
B. Chronic gastritis.
C. Chronic pancreatitis.
D.Chronic colitis.
E. Ulcer disease. +

4. Male 18 years old, at the first time was diagnosed duodenum ulcer disease. Test for H. Pilory positive. pH of gastric juice – 1,0. What scheme of treatment is most effective?
A. Clarithromycin + omeprazole. +
B. Amoxicillin + Cvamatel.
C. De-Nol + oxacillin.
D. De-Nol + trihopol.
E. Omeprazole+ cimetidine.
5. Patient 35y.o. Complaints: weakness, weight loss, aversion to meat, heaviness in stomach.Objective: pale skin, duffuse pain in epigastric region. CBC: Hb 82 g/l, ESR 52 mm/h; positive reaction for occult blood in stool. Fibrogastroduodenoscopy - in the stomach fundus - ulcer with infiltrative shaft. What is most likely diagnosis?
A. Stomach ulcer.
B. Stomach cancer. +
C. Duodenal ulcer.
D. Chronic gastritis.
E. Chronic pancreatitis.
6. Patient with duodenum ulcer disease was revealed the presence of H. Pilory. During combined therapy, stool became black-green colour. Name the drug, which caused this change.
A. Metronidazole.
B. Omeprazole.
C. De-Nol. +
D. Amoxicillin.
E. Actovegin.
7. Patient with duodenum ulcer disease complaints on pain after meal with irradiation to the back. Weight loss till 6 kg for 6 month. Endoscopy – bulbus ulcer with deformation. How you can explain these complaints?
A. Penetration. +
B. Perforation.
C. Duodenostasis.
D. Pilorostenosis.
E. Malignization.
8. Patient suffers from ulcer desease. For last 6 month complaints with epigastral pain, nausea, lack of appetite, weight loss, aversion to meat. Objective: low nutrition, above the left clavicle palpable lymph node.Which disease should be excluded first?
A. Stomach cancer. +
B. Cancer of pancreas.
C. Chronic hepatitis.
E. Chronic gastritis.
D. Cancer of gall bladder.
9. The patient complaints onintensive epigastric pain, occurred 1-1,5 hour after meal. For 11 years suffers from ulcer disease. Objective: palpation - pain in the right epigastral region. Ps 70 bpm, BP 120/80 mmHg. What indicators of intragastral pH-metry in the stomach fundus are more characteristic of the patient's disease?
A. pH =1,0-2,0. +
B. pH =3,0-4,0.
C. pH =4,0-5,0.
D. pH =5,0-6,0.
E. pH =6,0-7,0.
10. Surgical treatment due to peptic ulcer is indicated in:
A. Always with a purpose to reducingsecretion .
B. Only in complicated cases. +
C. Stomach ulcer.

D. H.Pilory-negative ulcer.
E. H.Pilory-positive ulcer.
III. Formation of professional skills, abilities:
3.1. content of tasks (tasks, clinical situations, etc.)
Case history #1. A 40-year-old man presents to his primary care physician with a 2-month history of intermittent upper abdominal pain. He describes the pain as a dull, gnawing ache. The pain sometimes wakes him at night, is relieved by food and drinking milk, and is helped partially by ranitidine. He had a similar but milder episode about 5 years ago, which was treated with omeprazole. Physical examination reveals a fit, apparently healthy man in no distress. The only abnormal finding is mild epigastric tenderness on palpation of the abdomen.
Task: Applicant should write diagnosis, plan of investigation, carry out differential diagnosis, prescribe treatment for this case history.
3.2. recommendations (instructions) for performing tasks (professional algorithms, orientation maps for the formation of practical skills, etc.)
Professional algorithms.
VII. Patient's examination.
During patient's examination applicants should keep such communicative skills:
1. Friendly face expression.
2. Kind voice tone.
3. Greetings, showing concern and respect about the patient.
4. Find out patient's complaints and anamnesis .
5. Explanation of investigation results.
6. Explanation of specific actions (hospitalization, carrying out investigations) which are planned to be performed in the future.
7. Finishing of the talk.

VIII. Patient's examination and investigation algorithm.

1. Student should perform palpation of epigastria area and make percussion for defining of lower border of stomach's great curvature.
2. It should be explained to patient which investigation will be held and indications for this investigation.
3. A doctor should receive patient's agreement on investigation.
4. A doctor should warn patient about possibilities of unpleasant feelings during oesophagogastroduodenoscopy or X-ray with barium contrast.
5. Results of investigation should be explained to a patient.
6. If the patient is aged ≥60 years old with dyspeptic symptoms, prompt endoscopy is indicated.
7. Barium radiography should be reserved for patients who are unable or unwilling to undergo endoscopy.
8. Non-invasive testing for H pylori (i.e., urea breath or stool antigen tests) in patients with dyspepsia who are aged under 60 years is recommended.
9. Histology and biopsy urease testing (rapid urease test) are performed on stomach biopsies obtained during endoscopy.
10. Endoscopy should be repeated after 6 to 8 weeks in patients with gastric ulcer to ensure ulcer healing and to rule out malignancy.
11. Fasting serum gastrin level should be checked if there are multiple duodenal ulcers (especially postbulbar) or in patient with ulcers and diarrhoea.

IX. Step-by-step algorithm of treatment.

1. A patient should informed be about necessity of the prescribed treatment.
2. Dosages, drugs intake regimens, duration of treatment, side effects of the prescribed therapy should be kindly explained to patient.
3. First-line treatment options for HP-positive ulcers include triple therapy (a proton-pump inhibitor plus clarithromycin, and amoxicillin) or quadruple therapy (a PPI plus bismuth plus tetracycline and metronidazole) is given for 14 days.

4. Check for eradication of H pylori 1 month after the end of therapy.
5. A cyclooxygenase (COX-2) inhibitor may be considered in preference to an NSAID to reduce the risk of gastroduodenal toxicity, including ulceration in Hp-negative ulcers. PPIs are the drug of choice for ulcer healing in this case.
6. A prostaglandin analogue such as misoprostol should be used in patients with NSAID-associated ulcers refractory to acid suppression therapy.
7. Most bleeding ulcers can be treated endoscopically.
8. Blood transfusion can be considered to resuscitate acute volume loss.

3.3. requirements for applicants work results.
As a results of studying applicants must perform the following:
-possess skills of communication and clinical examination of a patient ulcer disease;
-collect data on patient complaints, medical history, life history;
-evaluate information about the diagnosis of ulcer disease using a standard procedure, based on the results of laboratory and instrumental studies. Determine the list of required clinical, laboratory and instrumental studies and evaluate their results;
- identify the leading clinical symptom or syndrome. Establish the most probable or syndrom diagnosis. Assign laboratory and instrumental investigations for patient. Carry out differential diagnosis ulcer disease. Establish preliminary and clinical diagnosis;
- determine the principles of treatment, the required regime of work/rest and alimentary regime of patients with ulcer disease;
- diagnose emergencies in the clinic of ulcer disease;
- define tactics and provide emergency medical care;
- perform an expertise of work capacity of patients with ulcer disease.

3.4. control materials for the final stage of the lesson.
Work 1
1. Collection of complaints, anamnesis, examination of a patient with gastric dyspepsia and chronic gastritis.
2. Detection of clinical and instrumental symptoms.
3. Grouping symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data (clinical analysis of blood, urine, biochemical analysis of blood, PPI - test, radiography of the esophagus and stomach with barium, FGDS, ECG, echocardiography, etc.).
6. Carrying out a differential diagnosis.
7. Formulation of the clinical diagnosis.
8. Write a prescription list for patients diagnosed with gastric dyspepsia and chronic gastritia, which would include diet and prescribed drugs.
9. Determining of the disability degree.
Work 2.
Assignment of differentiated treatment programs according to the clinical protocol of medical care.
Work 3.
Work in the Internet, in the reading room of the department library with thematic literature.
The student fills in the protocol of the patient's examination. An example of the initial examination of the patient is attached.
The tests for self-control with standard answers.
1. A 33 y.o. male patient was admitted to a hospital. A patient is pale, at an attempt to stand up he complains of strong dizziness. There was vomiting like coffee-grounds approximately hour ago. BP- 90/60 mm Hg, pulse- 120 b/min. In anamnesis, a patient has suffered from ulcer of the

stomach, painless form during 4 years. An ulcer was exposed at gastrofiberoscopy. Your diagnosis:

A Ulcer of stomach, complicated with bleeding
B Ulcer of duodenum, complicated with bleeding
C Erosive gastritis
D Acute pleurisy
E Acute myocardial infarction, abdominal form

2. In autumn a 25-year-old patient developed stomach ache arising 1,5-2 hours after having mealsand at night. He complains of pyrosis and constipation. The pain is getting worse after consuming spicy, salty and sour food, it can be relieved by means of soda and hot-water bag. The patient has been suffering from this disease for a year. Objectively: furred moist tongue. Abdomen palpation reveals epigastrial pain on the right, resistance of abdominal muscles in the same region. What is the most likely diagnosis?

A Chronic cholecystitis
B Duodenal ulcer
C Diaphragmatic hernia
D Stomach ulcer
E Chronic pancreatitis

3.A 51 y.o. woman complains of dull pain in the right subcostal area and epigastric area, nausea, appetite decline during 6 months. There is a history of gastric peptic ulcer. On examination: weight loss, pulse is 70 bpm, AP is 120/70 mm Hg. Diffuse tenderness and resistance of muscles on palpation.There is a hard lymphatic node 1x1cm in size over the left clavicle. What method of investigation will be the most useful?

A pH-metry
B Ultrasound examination of abdomen
C Esophagogastroduodenoscopy with biopsy
D Ureatic test
E Stomach X-ray

4. A 43-year-old male patient undergoing treatment for peptic ulcer complains of weakness, dizziness, coffee-ground vomiting, melena. After administration of haemostatics the patient's condition has not improved, fresh blood has shown up in the vomit, skin bruises of different sizes have appeared. In blood: thrombocytes – $50x10^9$/l, Lee-White clotting time - 35 minutes, APTT - 80 seconds. In this case it is most rational to administer the following preparation:

A Rheopolyglucinum
B Heparin
C Fibrinogen
D Fresh frozen plasma
E Vikasol

5. A 60-year-old patient complains of nearly permanent sensation of heaviness and fullness in the epigastrium, that increases after eating, foul-smelling eructation, occasional vomiting with food consumed 1-2 days ago, weight loss. 12 years ago he was found to have an ulcer of pyloric channel. The patient has taken ranitidine for periodic hunger pain. The patient's condition has been deteriorating over the last 3 months. Objectively: splashing sound in the epigastrium is present. What kind of complication is it?

A Malignization of gastric ulcer
B Penetration of gastric ulcer
C Functional pyloric spasm
D Foreign body in the stomach (bezoar)
E Pyloric stenosis

6. A patient has undergone an operation on account of perforated ulcer of stomach, terminal phase of diffuse peritonitis and endotoxic shock. In the post-operative period he is prescribed artificial pulmonary ventilation with 60% oxygen inhalation. Blood gases: PaO_2- 70-78 mm Hg, hypoxemy

doesn't ecrease, CVP (central venous pressure) - 150-180 mm of water column, AP- 90/60 mm Hg (against the backgound of taking big doses of dopamine). Radiogram shows diffuse pulmonary infiltration. What cause the refractory arterial hypoxemia?
A Respiratory distress syndrome
B Bilateral pneumonia
C Pneumothorax
D Mendelson's syndrome
E Pulmonary edema
7. A 32 year old patient complains about heartburn and dull pain in the epigastrium that appear 2-3 hours after meal. Exacerbations happen in spring and in autumn. The patient has food intolerance of eggs and fish. Objectively: stomach palpation reveals painfulness in the gastroduodenal area. Electrophasoduodenoscopy revealed a 5 mm ulcer on the anterior wall of duodenum. Urease test is positive. What is the most probable leading mechanism of disease development?
A Dietary allergy
B Chelicobacterial infection
C Autoantibody production
D Reduced prostaglandin synthesis
E Disorder of gastric motor activity
8. A 42 y.o. man who has been ill with duodenal ulcer for 20 years complains of getting a sense of heaviness in stomach after meal, foul-smelling eructation, vomiting, weight loss. Objectively: his state is relatively satisfactory, tissue turgor is diminished. On palpation the abdomen is soft, there are no symptoms of peritenium irritation, "splashing sounds" in epigastrium. Defecation - once in 3 days. What complication corresponds with the patient's state and described clinical presentations?
A Stomach cancer
B Concealed ulcer perforation
C Ulcerative pyloric stenosis
D Ulcer penetration
E Chronic pancreatitis
9. A 23-year-old patient complains of a dull ache, sensation of heaviness and distension in the epigastrium immediately after meals, foul-smelling eructation; dry mouth, empty stomach nausea, diarrhoea. Objectively: the skin is pale, the patient is of thin build. Abdomen is soft on palpation, there is epigastric pain. The liver does not extend beyond the costal arch. In blood: Hb - 110 g/l, RBCs - $3{,}4x10^{12}$/l, WBC count is normal. ESR - 16 mm/h. What is the most informative study that will allow make a diagnosis?
A pH-metry
B Esophageal gastroduodenoscopy
C Study of gastric juice
D X-ray of digestion organs
E Duodenal probing
10. A 27 y.o. man complained of aching epigastric pain right after meal, heartburn and nausea. Stomach endoscopy revealed a large amount of mucus, hyperemia and edema of mucous membrane in gastric fundus with areas of atrophy. Make a diagnosis.
A Menetrier's disease
B Chronic gastritis of type B
C Peptic ulcer of stomach
D Chronic gastritis of type C
EChronic gastritis of type A
Standard answers: 1-A, 2-B,3-C, 4-D, 5-E, 6-A, 7-B, 8-C, 9-D, 10-E.

IV. Summarizing, announcing the final grade, announcing the task for the next lesson.
Recommended resources:
- Basic literature source:

1. Managing peptic ulcer in adults. Nice Pathways 2019.
2. Malfertheiner P, Megraud F, O'Morain C et al Management of Helicobacter pylori infection – the Maastricht V / Florence Consensus Report // Gut. – 2017. – Vol.66. – P. 6-30

- Additional literature source:

1. Best LM, Takwoingi Y, Siddique S, et al. Non-invasive diagnostic tests for Helicobacter pylori infection. Cochrane Database Syst Rev. 2018;(3):CD012080.

Appendix 1

Example of the primary examination of the patient

Passport data: name and surname, age

Complaints:

hunger, late and night pains in the epigastric region, heartburn, belching, a feeling of "scorched" tongue, which intensifies closer to the evening. Appetite is normal and even increased.

Anamnesis morbi

Ill since adolescence, exacerbations are often in the autumn, eats irregularly, smokes a lot. Previously, he did not seek for medical help and wasn't examined.

Anamnesis vitae

Living conditions are satisfactory. Botkin's disease, tuberculosis, sexually transmitted diseases, malaria denies.

Professional anamnesis: not burdened.

Hereditary history is not burdened.

Pave not been in contact with infectious patients for the last 3 days. He has not left the country in the last 3 years.

***Hereditary history**: not burdened*

Neurological history

At the time of examination signs of focal neurological symptoms were not detected.

***Allergic history**: not burdened*

Epidemiology

Tuberculosis, malaria, viral hepatitis, Botkin's disease, veneral disease, HIV, AIDS, pediculosis – denies.

***Oncoanamnesis**: denies.*

***Insurance anamnesis**: There is no need to issue a seak leave, for the last 12 months a seak leave document has not been issued in this regard.*

***Postponed operations**: denies.*

***Bad habits**: smokes for 10 years, 1 pack a day*

Examination of organ systems:

GENERAL Condition: satisfactory

CONSCIOUSNESS: clear

Body shape: hypostenic

Fatness: low nutrition

POSITION OF THE PATIENT: active

BODY TEMPERATURE: 36.6 C. Signs of alcohol intoxication - no

SKIN: Skin of normal color, clean. Tissue turgor is normal. Skin pigmentation: depigmentation - no. Rash: no; other changes in the skin: no.

Visible mucous membranes: Normal color

LYMPH NODES: not enlarged

THYROID GLAND: no pathology

Oncological examination was performed, no visual forms of oncopathology were detected

Cardiovascular system:

PERCUSSION OF THE HEART: the limits of relative cardiac dullness: right on the right edge of the sternum, upper -III rib on the left parasternalis line, left - 1 cm outward from the left mediaclavicularis line in the V intercostal space
HEART activity: rhythmic, heart rate - 74 per 1 min. Pulse 74 in 1 min. Heart tones: muffled
HEART MURMURS: no
EDEMA: no
BP 125 / 85 mm Hg
EXAMINATION OF ARTERIES: no pathology
VEIN STUDY: no pathology
RESPIRATORY SYSTEM:
BREATHING: no dyspnea at rest, RR 16 in 1 min.
Sputum: no
CHEST: cylindrical, not deformed. Intercostal spaces: NOT smoothed. Participation of additional muscles: no, RR – 16 in 1 min. SpO2 = 98%
Percussion over the lungs: clear lung sound.
PULMONARY AUSCULTATION: vesicular breathing over both lungs. Pleural friction noise - no
DIGESTIVE SYSTEM:
TONGUE: wet; covered with white plaque
Tonsils: not enlarged
STOMACH: participates in the act of breathing. No hernia. Pulsation in the epigastrium - no. There is no dilation of the subcutaneous veins
Palpation: moderately painful in the pyloroduodenal region
Pathological symptoms: not detected
Liver: not enlarged
Gallbladder: not palpable
Pancreas: painless
Spleen: not palpable,
PERCUTIONAL SOUND OVER THE ABDOMINAL CAVITY: unchanged,
FECES: normal, no pathological impurities
URINARY SYSTEM:
Palpation of the kidneys: not palpable
Pasternatsky's symptom is negative on both sides.
Urination: free, painless, frequency per day: 3-4 times.
Urinary incontinence: no.
SENSES:
SIGHT: not violated (OU). There is no other pathology
HEARING: normal, no deafness, pain: no. Tinnitus: no.
Musculoskeletal system:
Pathology of the musculoskeletal system was not detected
On the basis of complaints, anamnesis, objective examination, it is possible to make a preliminary diagnosis:
Duodenal ulcer
Plan of investigation
general blood test, general urine test, glycemia level (8.00, 13.00, 17.00, 21.00)
Biochemistry: liver tests, glucose, transaminases, protein, lipid spectrum, coagulogram, amylase, AF, LDG, GGT, CPK, serum iron, potassium, CRP, seromucoid, RF, ASLO.
ECG, FGDS with biopsy, helpil-test, ultrasound of abdominal organs
Consultation with a gastroenterologist.
Treatment plan
Normalization of lifestyle
Diet
Drug therapy:

- Omeprazole 20 mg - 1 tab. x 2 times/day, 20 minutes before eating
- Eradication of Helicobacter pylori if there is a positive helpil test
Scheme of eradication:
1. *Omeprazole 20 mg x 2 times a day*
2. *Amoxicillin 1000 mg x 2 times a day*
3. *Clarithromycin 500 mg x 2 times a day for 10-14 days*

At inefficiency of three-component therapy:
4. *Omeprazole 20 mg x 2 times a day*
5. *Bismuth subcitrate 120 mg x 4 times a day*
6. *Metronidazole 500 mg x 3 times a day*
7. *Tetracycline 500 mg x 4 times a day for 10-14 days*

Appendix 2

Tests of basic knowledge level in KROK format
Theme 20. Ulcer disease and other peptic ulcer of stomach and duodenum

1. A 60-year-old patient complains of nearly permanent sensation of heaviness and fullness in the epigastrium, that increases after eating, foul-smelling eructation, occasional vomiting with food consumed 1-2 days ago, weight loss. 12 years ago he was found to have an ulcer of pyloric channel. The patient has taken ranitidine for periodic hunger pain. The patient's condition has been deteriorating over the last 3 months. Objectively: splashing sound in the epigastrium is present. What kind of complication is it?
A Malignization of gastric ulcer
B Penetration of gastric ulcer
C Functional pyloric spasm
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E Pyloric stenosis

2. A 43-year-old male patient undergoing treatment for peptic ulcer complains of weakness, dizziness, coffee-ground vomiting, melena. After administration of haemostatics the patient's condition has not improved, fresh blood has shown up in the vomit, skin bruises of different sizes have appeared. In blood: thrombocytes – $50x10^9$/l, Lee-White clotting time - 35 minutes, APTT - 80 seconds. In this case it is most rational to administer the following preparation:
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A pH-metry
B Ultrasound examination of abdomen
C Esophagogastroduodenoscopy with biopsy
D Ureatic test
E Stomach X-ray

4. In autumn a 25-year-old patient developed stomach ache arising 1,5-2 hours after having mealsand at night. He complains of pyrosis and constipation. The pain is getting worse after consuming spicy, salty and sour food, it can be relieved by means of soda and hot-water bag. The patient has been suffering from this disease for a year. Objectively: furred moist tongue. Abdomen

palpation reveals epigastrial pain on the right, resistance of abdominal muscles in the same region. What is the most likely diagnosis?

A Chronic cholecystitis
B Duodenal ulcer
C Diaphragmatic hernia
D Stomach ulcer
E Chronic pancreatitis

5. A 33 y.o. male patient was admitted to a hospital. A patient is pale, at an attempt to stand up he complains of strong dizziness. There was vomiting like coffee-grounds approximately hour ago. BP- 90/60 mm Hg, pulse- 120 b/min. In anamnesis, a patient has suffered from ulcer of the stomach, painless form during 4 years. An ulcer was exposed at gastrofiberoscopy. Your diagnosis:

A Ulcer of stomach, complicated with bleeding
B Ulcer of duodenum, complicated with bleeding
C Erosive gastritis
D Acute pleurisy
E Acute myocardial infarction, abdominal form

6. A 27 y.o. man complained of aching epigastric pain right after meal, heartburn and nausea. Stomach endoscopy revealed a large amount of mucus, hyperemia and edema of mucous membrane in gastric fundus with areas of atrophy. Make a diagnosis.

A Menetrier's disease
B Chronic gastritis of type B
C Peptic ulcer of stomach
D Chronic gastritis of type C
EChronic gastritis of type A

7. A 23-year-old patient complains of a dull ache, sensation of heaviness and distension in the epigastrium immediately after meals, foul-smelling eructation; dry mouth, empty stomach nausea, diarrhoea. Objectively: the skin is pale, the patient is of thin build. Abdomen is soft on palpation, there is epigastric pain. The liver does not extend beyond the costal arch. In blood: Hb - 110 g/l, RBCs - $3{,}4x10^{12}$/l, WBC count is normal. ESR - 16 mm/h. What is the most informative study that will allow make a diagnosis?

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B Concealed ulcer perforation
C Ulcerative pyloric stenosis
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A Dietary allergy

B Chelicobacterial infection
C Autoantibody production
D Reduced prostaglandin synthesis
E Disorder of gastric motor activity

10. A patient has undergone an operation on account of perforated ulcer of stomach, terminal phase of diffuse peritonitis and endotoxic shock. In the post-operative period he is prescribed artificial pulmonary ventilation with 60% oxygen inhalation. Blood gases: PaO_2- 70-78 mm Hg, hypoxemy doesn't ecrease, CVP (central venous pressure) - 150-180 mm of water column, AP- 90/60 mm Hg (against the backgound of taking big doses of dopamine). Radiogram shows diffuse pulmonary infiltration. What cause the refractory arterial hypoxemia?

A Respiratory distress syndrome
B Bilateral pneumonia
C Pneumothorax
D Mendelson's syndrome
E Pulmonary edema

Practical lesson #21

Theme: Disease of small bowel: celiac disease and other enteropathy.

Goal:

To study:

- Etiology, pathogenesis of celiac disease, Wipple's disease, disucrose insufficiency, classification, clinic, complications, diagnosis and treatment.
- General and dietary recommendations in different enteropaties.
- Classification and pharmacological peculiarity of drugs, which are used in enterology.

Basic concepts. Coeliac disease: definition, epidemiology, aetiology. Pathophysiology. Classification. Diagnosis and differential diagnostics. Treatment. Complications.

Malabsorption is inadequate assimilation of dietary substances due to defects in digestion, absorption, or transport.

Malabsorption can affect macronutrients (eg, proteins, carbohydrates, fats), micronutrients (eg, vitamins, minerals), or both, causing excessive fecal excretion, nutritional deficiencies, and GI symptoms. Malabsorption may be global, with impaired absorption of almost all nutrients, or partial (isolated), with malabsorption of only specific nutrients.

Pathophysiology

Digestion and absorption occur in three phases: (1) intraluminal hydrolysis of fats, proteins, and carbohydrates by enzymes—bile salts enhance the solubilization of fat in this phase; (2) digestion by brush border enzymes and uptake of end-products; and (3) lymphatic transport of nutrients. The term malabsorption is commonly used when any of these phases is impaired, but, strictly speaking, impairment of phase 1 is maldigestion rather than malabsorption.

Fats:

Pancreatic enzymes (lipase and colipase) split long-chain triglycerides into fatty acids and monoglycerides, which combine with bile acids and phospholipids to form micelles that pass through jejunal enterocytes. Absorbed fatty acids are resynthesized and combined with protein, cholesterol, and phospholipid to form chylomicrons, which are transported by the lymphatic system. Medium-chain triglycerides are absorbed directly.

Unabsorbed fats trap fat-soluble vitamins (A, D, E, K) and possibly some minerals, causing deficiency. Bacterial overgrowth results in deconjugation and dehydroxylation of bile salts, limiting the absorption of fats. Unabsorbed bile salts stimulate water secretion in the colon, causing diarrhea.

Carbohydrates:

The pancreatic enzyme amylase and brush border enzymes on microvilli lyse carbohydrates and disaccharides into constituent monosaccharides. Colonic bacteria ferment unabsorbed carbohydrates into CO_2, methane, H_2, and short-chain fatty acids (butyrate, propionate, acetate, and lactate). These fatty acids cause diarrhea. The gases cause abdominal distention and bloating.

Proteins:

Gastric pepsin initiates digestion of proteins in the stomach (and also stimulates release of cholecystokinin that is critical to the secretion of pancreatic enzymes). Enterokinase, a brush border enzyme, activates trypsinogen into trypsin, which converts many pancreatic proteases into their active forms. Active pancreatic enzymes hydrolyze proteins into oligopeptides, which are absorbed directly or hydrolyzed into amino acids.

Etiology

Malabsorption has many causes. Some malabsorptive disorders (eg, celiac disease) impair the absorption of most nutrients, vitamins, and trace minerals (global malabsorption); others (eg, pernicious anemia) are more selective.

Pancreatic insufficiency causes malabsorption if > 90% of function is lost. Increased luminal acidity (eg, Zollinger-Ellison syndrome) inhibits lipase and fat digestion. Cirrhosis and cholestasis reduce hepatic bile synthesis or delivery of bile salts to the duodenum, causing malabsorption.

Causes of Malabsorption

Mechanism	Cause
Inadequate gastric mixing, rapid emptying, or both	Billroth II gastrectomy Gastrocolic fistula Gastroenterostomy
Insufficient digestive agents	Biliary obstruction and cholestasis Cirrhosis Chronic pancreatitis Cholestyramine-induced bile acid loss Cystic fibrosis Lactase deficiency Pancreatic cancer Pancreatic resection Sucrase-isomaltase deficiency
Abnormal milieu	Abnormal motility secondary to diabetes, scleroderma, hypothyroidism, or hyperthyroidism Bacterial overgrowth due to blind loops (deconjugation of bile salts), diverticula in the small intestine Zollinger-Ellison syndrome (low duodenal pH)
Acutely abnormal epithelium	Acute intestinal infections Alcohol Neomycin
Chronically abnormal epithelium	Amyloidosis Celiac disease Crohn disease Ischemia Radiation enteritis Tropical sprue Whipple disease
Short bowel	Intestinal resection (eg, for Crohn disease, volvulus, intussusception, or infarction) Jejunoileal bypass for obesity
Impaired transport	Abetalipoproteinemia Addison disease Blocked lacteals due to lymphoma or TB Intrinsic factor deficiency (as in pernicious anemia) Lymphangiectasia

Symptoms and Signs

The effects of unabsorbed substances, especially in global malabsorption, include diarrhea, steatorrhea, abdominal bloating, and gas. Other symptoms result from nutritional deficiencies. Patients often lose weight despite adequate food intake.

Chronic diarrhea is the most common symptom and is what usually prompts evaluation of the patient. Steatorrhea—fatty stool, the hallmark of malabsorption—occurs when > 7 g/day of fat are excreted. Steatorrhea causes foul-smelling, pale, bulky, and greasy stools.

Severe vitamin and mineral deficiencies occur in advanced malabsorption; symptoms are related to the specific nutrient deficiency. Vitamin B_{12}deficiency may occur in blind loop syndrome or after extensive resection of the distal ileum or stomach. Iron deficiency may be the only symptom in a patient with mild malabsorption.

Amenorrhea may result from undernutrition and is an important manifestation of celiac disease in young women.

Diagnosis

- Diagnosis typically clinically apparent from a detailed patient history
- Blood tests to screen for consequences of malabsorption
- Stool fat testing to confirm malabsorption (if unclear)
- Cause diagnosed with endoscopy, contrast x-rays, or other tests based on findings

Malabsorption is suspected in a patient with chronic diarrhea, weight loss, and anemia. The etiology is sometimes obvious. For example, patients with malabsorption due to chronic pancreatitis usually have had prior bouts of acute pancreatitis. Patients with celiac disease can present with classic lifelong diarrhea exacerbated by gluten products and may have dermatitis herpetiformis. Those with cirrhosis and pancreatic cancer can present with jaundice. Abdominal distention, excessive flatus, and watery diarrhea occurring 30 to 90 min after carbohydrate ingestion suggest deficiency of a disaccharidase enzyme, usually lactase. Previous extensive abdominal operations suggest short bowel syndrome.

If the history suggests a specific cause, testing should be directed to that condition. If no cause is readily apparent, blood tests can be used as screening tools (eg, CBC, RBC indices, ferritin, vitamin B_{12}, folate, Ca, albumin, cholesterol, PT). Test results may suggest a diagnosis and direct further investigation.

Symptoms of Malabsorption

Symptom	**Malabsorbed Nutrient**
Anemia (hypochromic, microcytic)	Iron
Anemia (macrocytic)	Vitamin B_{12}, folate
Bleeding, bruising, petechiae	Vitamins K and C
Carpopedal spasm	Ca, Mg
Edema	Protein
Glossitis	Vitamins B_2 and B_{12}, folate, niacin, iron
Night blindness	Vitamin A
Pain in limbs, bones, pathologic fractures	K, Mg, Ca, vitamin D
Peripheral neuropathy	Vitamins B_1, B_6, B_{12}

Macrocytic anemia should prompt measurement of serum folate and B_{12} levels. Folate deficiency is common in mucosal disorders involving the proximal small bowel (eg, celiac disease, tropical sprue, Whipple disease). Low B_{12} levels can occur in pernicious anemia, chronic pancreatitis, bacterial overgrowth, and terminal ileal disease. A combination of low B_{12} and high folate levels is suggestive of bacterial overgrowth, because intestinal bacteria use vitamin B_{12} and synthesize folate.

Microcytic anemia suggests iron deficiency, which may occur with celiac disease. Albumin is a general indicator of nutritional state. Low albumin can result from poor intake, decreased synthesis in cirrhosis, or protein wasting. Low serum carotene (a precursor of vitamin A) suggests malabsorption if intake is adequate.

Confirming malabsorption:

Tests to confirm malabsorption are appropriate when symptoms are vague and the etiology is not apparent. Most tests for malabsorption assess fat malabsorption because it is relatively easy to measure. Confirmation of carbohydrate malabsorption is not helpful once steatorrhea is documented. Tests for protein malabsorption are rarely used because fecal nitrogen is difficult to measure.

Direct measurement of fecal fat from a 72-h stool collection is the gold standard test for establishing steatorrhea but unnecessary with gross steatorrhea of obvious cause. However, this test is available routinely in only a few centers. Stool is collected for a 3-day period during which the patient consumes$\geq$ 100 g fat/day. Total fat in the stool is measured. Fecal fat > 7 g/day is abnormal. Although severe fat malabsorption (fecal fat $\geq$ 40 g/day) suggests pancreatic insufficiency or small-

bowel mucosal disease, this test cannot determine the specific cause of malabsorption. Because the test is messy, unpleasant, and time consuming, it is unacceptable to most patients and difficult to do.

Sudan III staining of a stool smear is a simple and direct, but nonquantitative, screening test for fecal fat. Acid steatocrit is a gravimetric assay done on a single stool sample; it has a reported high sensitivity and specificity (using 72-h collection as the standard). Near-infrared reflectance analysis (NIRA) simultaneously tests stool for fat, nitrogen, and carbohydrates and may become the preferred test in the future; this test is currently available in only a few centers.

Measurement of elastase and chymotrypsin in the stool can also help differentiate pancreatic and intestinal causes of malabsorption; both are decreased in pancreatic exocrine insufficiency, whereas both are normal in intestinal causes.

The D-xylose absorption test can be done if the etiology is not obvious; however, it is currently rarely used because of the advent of advanced endoscopic and imaging tests. Although it can noninvasively assess intestinal mucosal integrity and help differentiate mucosal from pancreatic disease, an abnormal D-xylose test result requires an endoscopic examination with biopsies of the small-bowel mucosa. As a result, small-bowel biopsy has replaced this test to establish intestinal mucosal disease.

D-Xylose is absorbed by passive diffusion and does not require pancreatic enzymes for digestion. A normal D-xylose test result in the presence of moderate to severe steatorrhea indicates pancreatic exocrine insufficiency rather than small-bowel mucosal disease. Bacterial overgrowth syndrome can cause abnormal results because the enteric bacteria metabolize pentose, thus decreasing the D-xylose available for absorption.

After fasting, the patient is given 25 g of D-xylose in 200 to 300 mL of water po. Urine is collected over 5 h, and a venous sample is obtained after 1 h. Serum D-xylose < 20 mg/dL or < 4 g in the urine sample indicates abnormal absorption. Falsely low levels can also occur in renal diseases, portal hypertension, ascites, or delayed gastric emptying time.

Diagnosing the cause of malabsorption:

More specific diagnostic tests (eg, upper endoscopy, colonoscopy, barium x-rays) are indicated to diagnose several causes of malabsorption.

Endoscopy with small-bowel biopsy is done when mucosal disease of the small bowel is suspected or if the D-xylose test result is abnormal in a patient with massive steatorrhea. Endoscopy allows visual assessment of small-bowel mucosa and helps direct biopsies to affected areas. Aspirate from the small bowel can be sent for bacterial culture and colony count to document bacterial overgrowth if there is clinical suspicion. Histologic features on small-bowel biopsy can establish the specific mucosal disease.

Small-bowel x-rays (eg, small-bowel follow-through, enteroclysis) can detect anatomic conditions that predispose to bacterial overgrowth. These include jejunal diverticula, fistulas, surgically created blind loops and anastomoses, ulcerations, and strictures. Abdominal flat plate x-rays may show pancreatic calcifications indicative of chronic pancreatitis. Barium contrast studies of the small bowel are neither sensitive nor specific but may show findings suggestive of mucosal disease (eg, dilated small-bowel loops, thinned or thickened mucosal folds, coarse fragmentation of the barium column). CT, magnetic resonance cholangiopancreatography (MRCP), and ERCP can establish the diagnosis of chronic pancreatitis.

Tests for pancreatic insufficiency (eg, secretin stimulation test, bentiromide test, pancreolauryl test, serum trypsinogen, fecal elastase, fecal chymotrypsin are done if history is suggestive but are not sensitive for mild pancreatic disease.

The ^{14}C-xylose breath test helps diagnose bacterial overgrowth. ^{14}C-xylose is given orally, and the exhaled $^{14}CO_2$ concentration is measured. Catabolism of ingested xylose by the overgrowth of flora causes $^{14}CO_2$ to appear in exhaled breath.

The H_2 breath test measures the exhaled H_2 produced by the bacterial degradation of carbohydrates. In patients with disaccharidase deficiencies, enteric bacteria degrade nonabsorbed carbohydrates in the colon, increasing exhaled H_2. The lactose-H_2 breath test is useful only to confirm lactase

deficiency and is not used as an initial diagnostic test in the evaluation of malabsorption. The ^{14}C-xylose and H_2 breath tests have replaced bacterial cultures of aspirates taken during endoscopy for diagnosis of bacterial overgrowth syndrome.

The Schilling test assesses malabsorption of vitamin B_{12}. Its 4 stages determine whether the deficiency results from pernicious anemia, pancreatic exocrine insufficiency, bacterial overgrowth, or ileal disease.

- Stage 1: The patient is given 1 μg of radiolabeled cyanocobalamin po concurrent with 1000 μg of nonlabeled cobalamin IM to saturate hepatic binding sites. A 24-h urine collection is analyzed for radioactivity; urinary excretion of < 8% of the oral dose indicates malabsorption of cobalamin.
- Stage 2: If stage 1 is abnormal, the test is repeated with the addition of intrinsic factor. Pernicious anemia is present if intrinsic factor normalizes absorption.
- Stage 3: Stage 3 is done after adding pancreatic enzymes; normalization in this stage indicates cobalamin malabsorption secondary to pancreatic insufficiency.
- Stage 4: Stage 4 is done after antimicrobial therapy with anaerobic coverage; normalization after antibiotics suggests bacterial overgrowth.

Cobalamin deficiency secondary to ileal disease or ileal resection results in abnormalities in all stages.

Tests for less common causes of malabsorption include serum gastrin (Zollinger-Ellison syndrome), intrinsic factor and parietal cell antibodies (pernicious anemia), sweat chloride (cystic fibrosis), lipoprotein electrophoresis (abetalipoproteinemia), and serum cortisol (Addison disease).

To diagnose bile acid malabsorption, which may occur with diseases of the terminal ileum (eg, Crohn disease, extensive resection of terminal ileum), patients can be given a therapeutic trial of a bile acid binding resin (eg, cholestyramine). Alternatively, the selenium homocholic acid taurine (SeHCAT) test can be done. In this test, ^{75}Se-labeled synthetic bile acid is given orally and, after 7 days, the retained bile acid is measured with a whole-body scan or gamma camera. If bile acid absorption is abnormal, retention is less than 5%.

Celiac disease

is an immunologically mediated disease in genetically susceptible people caused by intolerance to gluten, resulting in mucosal inflammation and villous atrophy, which causes malabsorption. Symptoms usually include diarrhea and abdominal discomfort. Diagnosis is by small-bowel biopsies showing characteristic though not specific pathologic changes of villous atrophy that resolve with a strict gluten-free diet.

Etiology

Celiac disease is a hereditary disorder caused by sensitivity to the gliadin fraction of gluten, a protein found in wheat; similar proteins are present in rye and barley. In a genetically susceptible person, gluten-sensitive T cells are activated when gluten-derived peptide epitopes are presented. The inflammatory response causes characteristic mucosal villous atrophy in the small bowel.

Epidemiology:

Celiac disease mainly affects people of northern European descent. Prevalence estimates based on serologic screens among blood donors (sometimes confirmed by biopsy) indicate the disorder may be present in about 1/300 in Europe, especially in Ireland and Italy, and perhaps 1/250 in some parts of the US. Current prevalence estimates in some regions are as high as 1/100.

The disease affects about 10 to 20% of 1st-degree relatives. Female:male ratio is 2:1. Onset is generally in childhood but may occur later.

Symptoms and Signs

The clinical presentation varies; no typical presentation exists. Some patients are asymptomatic or have only signs of nutritional deficiency. Others have significant GI symptoms.

Celiac disease can manifest in infancy and childhood after introduction of cereals into the diet. The child has failure to thrive, apathy, anorexia, pallor, generalized hypotonia, abdominal distention,

and muscle wasting. Stools are soft, bulky, clay-colored, and offensive. Older children may present with anemia or failure to grow normally.

In adults, lassitude, weakness, and anorexia are most common. Mild and intermittent diarrhea is sometimes the presenting symptom. Steatorrhea ranges from mild to severe (7 to 50 g of fat/day). Some patients have weight loss, rarely enough to become underweight. Anemia, glossitis, angular stomatitis, and aphthous ulcers are usually seen in these patients. Manifestations of vitamin D and Ca deficiencies (eg, osteomalacia, osteopenia, osteoporosis) are common. Both men and women may have reduced fertility; women may not have menstrual periods.

About 10% of patients have dermatitis herpetiformis, an intensely pruritic papulovesicular rash that is symmetrically distributed over the extensor areas of the elbows, knees, buttocks, shoulders, and scalp. This rash can be induced by a high-gluten diet. Celiac disease is also associated with diabetes mellitus, autoimmune thyroid disease, and Down syndrome.

Diagnosis

- ✓ Serologic markers
- ✓ Small-bowel biopsy

The diagnosis is suspected clinically and by laboratory abnormalities suggestive of malabsorption. Family incidence is a valuable clue. Celiac disease should be strongly considered in a patient with iron deficiency without obvious GI bleeding.

Confirmation requires a small-bowel biopsy from the second portion of the duodenum. Findings include lack or shortening of villi (villous atrophy), increased intraepithelial cells, and crypt hyperplasia. However, such findings can also occur in tropical sprue, severe intestinal bacterial overgrowth, eosinophilic enteritis, lactose intolerance, and lymphoma.

Because biopsy lacks specificity, serologic markers can aid diagnosis. Anti-tissue transglutaminase antibody (AGA) and anti-endomysial antibody (EMA—an antibody against an intestinal connective tissue protein) have sensitivity and specificity > 90%. These markers can also be used to screen populations with high prevalence of celiac disease, including 1st-degree relatives of affected patients and patients with diseases that occur at a greater frequency in association with celiac disease. If either test is positive, the patient should have a diagnostic small-bowel biopsy. If both are negative, celiac disease is extremely unlikely. These antibodies decrease in titer in patients on a gluten-free diet and thus are useful in monitoring dietary adherence.

Other laboratory abnormalities often occur and should be sought. They include anemia (iron-deficiency anemia in children and folate-deficiency anemia in adults); low albumin, Ca, K, and Na; and elevated alkaline phosphatase and PT.

Malabsorption tests are not specific for celiac disease. If done, common findings include steatorrhea of 10 to 40 g/day and abnormal results with D-xylose and (in severe ileal disease) Schilling tests.

Prognosis

Mortality is 10 to 30% without a gluten-free diet. With proper diet, mortality is < 1%, mainly in adults who already have severe disease at diagnosis. Complications include refractory disease, collagenous sprue, and intestinal lymphomas. Intestinal lymphomas affect 6 to 8% of patients with celiac disease, usually manifesting after 20 to 40 yr of disease. The incidence of other GI cancers (eg, carcinoma of the esophagus or oropharynx, small-bowel adenocarcinoma) also increases. Adherence to a gluten-free diet can significantly reduce the risk of cancer.

Treatment

- ✓ Gluten-free diet
- ✓ Supplements to replace any serious deficiencies

Treatment is a gluten-free diet (avoiding foods containing wheat, rye, or barley). Gluten is so widely used (eg, in commercial soups, sauces, ice creams, hot dogs) that a patient needs a detailed list of foods to avoid. Patients are encouraged to consult a dietitian and join a celiac support group. The response to a gluten-free diet is usually rapid, and symptoms resolve in 1 to 2 wk. Ingesting even small amounts of food containing gluten may prevent remission or induce relapse.

Small-bowel biopsy should be repeated after 3 to 4 mo of a gluten-free diet. If abnormalities persist, other causes of villous atrophy (eg, lymphoma) should be considered. Lessening of symptoms and improvement in small-bowel morphology are accompanied by a decrease in AGA and EMA titers.

Supplementary vitamins, minerals, and hematinics may be given, depending on the deficiencies. Mild cases may not require supplementation, whereas severe cases may require comprehensive replacement. For adults, replacement includes ferrous sulfate300 mg po once/day to tid, folate 5 to 10 mg po once/day, Ca supplements, and any standard multivitamin. Sometimes children (but rarely adults) who are seriously ill on initial diagnosis require bowel rest and TPN.

If a patient responds poorly to gluten withdrawal, either the diagnosis is incorrect or the disease has become refractory. Corticosteroids can control symptoms in refractory disease.

Key Points

- ✓ Celiac disease involves an inflammatory response to gluten that causes villous atrophy and malabsorption.
- ✓ People of northern European heritage are most often affected.
- ✓ Suspect the diagnosis if the serologic markers anti-tissue transglutaminase antibody and anti-endomysial antibody are present and confirm the diagnosis with a small-bowel biopsy.
- ✓ Instruct the patient to follow a gluten-free diet and replace any vitamin or mineral deficiencies.

Carbohydrate intolerance

is the inability to digest certain carbohydrates due to a lack of one or more intestinal enzymes. Symptoms include diarrhea, abdominal distention, and flatulence. Diagnosis is clinical and by an H_2 breath test. Treatment is removal of the causative disaccharide from the diet.

Pathophysiology

Disaccharides are normally split into monosaccharides by disaccharidases (eg, lactase, maltase, isomaltase, sucrase [invertase]) located in the brush border of small-bowel enterocytes. Undigested disaccharides cause an osmotic load that attracts water and electrolytes into the bowel, causing watery diarrhea. Bacterial fermentation of carbohydrates in the colon produces gases (H_2, CO_2, and methane), resulting in excessive flatus, bloating and distention, and abdominal pain.

Etiology

Enzyme deficiencies can be congenital, acquired (primary), or secondary. Congenital deficiencies (eg, of lactase or sucrase-isomaltase) are rare.

Acquired lactase deficiency (primary adult hypolactasia) is the most common form of carbohydrate intolerance. Lactase levels are high in neonates, permitting digestion of milk; in most ethnic groups (80% of blacks and Hispanics, > 90% of Asians), the levels decrease in the post-weaning period rendering older children and adults unable to digest significant amounts of lactose. However, 80 to 85% of whites of Northwest European descent produce lactase throughout life and are thus able to digest milk and milk products. It is unclear why the normal state of > 75% of the world's population should be labeled a “deficiency.”

Secondary lactase deficiency occurs in conditions that damage the small-bowel mucosa (eg, celiac disease, tropical sprue, acute intestinal infections). In infants, temporary secondary disaccharidase deficiency may complicate enteric infections or abdominal surgery. Recovery from the underlying disease is followed by an increase in activity of the enzyme.

Symptoms and Signs

Symptoms and signs are similar in all disaccharidase deficiencies. A child who cannot tolerate lactose develops diarrhea after ingesting significant amounts of milk and may not gain weight. An affected adult may have watery diarrhea, bloating, excessive flatus, nausea, borborygmi, and abdominal cramps after ingesting lactose. The patient often recognizes early in life that dairy causes GI problems and avoids eating dairy products. Symptoms typically require ingestion of more than the equivalent of 250 to 375 mL (8 to 12 oz) of milk. Diarrhea may be severe enough to purge other nutrients before they can be absorbed. Symptoms may be similar to and can be confused with irritable bowel syndrome.

Diagnosis

- ✓ Clinical diagnosis
- ✓ H_2 breath test for confirmation

Lactose intolerance can usually be diagnosed with a careful history supported by dietary challenge. Patients usually have a history of diarrhea and/or gas after ingestion of milk and dairy foods; other symptoms, such as rash, wheezing, or other anaphylactic symptoms (particularly in infants and children), suggest a cow's milk allergy. Milk allergy is rare in adults and also may cause vomiting and symptoms of esophageal reflux, which are not manifestations of carbohydrate intolerance. The diagnosis is also suggested if the stool from chronic or intermittent diarrhea is acidic (pH < 6) and can be confirmed by an H_2 breath or a lactose tolerance test.

In the H_2 breath test, 50 g of lactose is given orally and the H_2 produced by bacterial metabolism of undigested lactose is measured with a breath meter at 2, 3, and 4 h postingestion. Most affected patients have an increase in expired H_2 of > 20 ppm over baseline. Sensitivity and specificity are >95%.

The lactose tolerance test is less sensitive, about 75%, although specificity is > 95%. Oral lactose (1.0 to 1.5 g/kg body weight) is given. Serum glucose is measured before ingestion and 60 and 120 min after. Lactose-intolerant patients develop diarrhea, abdominal bloating, and discomfort within 20 to 30 min, and their serum glucose levels do not rise to > 20 mg/dL (< 1.1 mmol/L) above baseline.

Treatment

Dietary restriction

Carbohydrate malabsorption is readily controlled by avoiding dietary sugars that cannot be absorbed (ie, following a lactose-free diet in cases of lactase deficiency). However, because the degree of lactose malabsorption varies greatly, many patients can ingest up to 375 mL (18 g of lactose) of milk daily without symptoms. Yogurt is usually tolerated because it contains an appreciable amount of lactase produced by intrinsic *Lactobacilli*. Cheese contains lower amounts of lactose than milk and is often tolerated, depending on the amount ingested.

For symptomatic patients wishing to drink milk, lactose in milk can be predigested by the addition of a commercially prepared lactase, and pretreated milk is now available. Enzyme supplements should be an adjunct to, not a substitute for, dietary restriction. Lactose-intolerant patients must take Ca supplements (1200 to 1500 mg/day).

Key Points

- ✓ Disaccharide deficiency (usually of lactase) can be acquired or, rarely, congenital.
- ✓ Undigested disaccharides, such as lactose, create an osmotic load that causes diarrhea.
- ✓ Intestinal bacteria metabolize some undigested disaccharides, producing gases that cause distention and flatus.
- ✓ Confirm clinical diagnosis by doing an H_2 breath test.
- ✓ Dietary restriction is usually adequate treatment.

Small-bowel bacterial overgrowth

can occur from alterations in intestinal anatomy or GI motility, or lack of gastric acid secretion. This condition can lead to vitamin deficiencies, fat malabsorption, and undernutrition. Diagnosis is by breath test or quantitative culture of intestinal fluid aspirate. Treatment is with oral antibiotics.

Under normal conditions, the proximal small bowel contains < 10^5 bacteria/mL, mainly gram-positive aerobic bacteria. This low bacterial count is maintained by normal peristalsis, normal gastric acid secretion, mucus, secretory IgA, and an intact ileocecal valve.

Etiology

Anatomic alterations of the stomach and/or small intestine promote stasis of intestinal contents, leading to bacterial overgrowth. Conditions that cause or require anatomic alterations include small-bowel diverticulosis, surgical blind loops, postgastrectomy states (especially in the afferent loop of a Billroth II), strictures, or partial obstruction. Intestinal motility disorders associated with diabetic

neuropathy, systemic sclerosis, amyloidosis, hypothyroidism, and idiopathic intestinal pseudo-obstruction can also impair bacterial clearance. Achlorhydria and idiopathic changes in intestinal motility may cause bacterial overgrowth in elderly people.

Pathophysiology

The excess bacteria consume nutrients, including carbohydrates and vitamin B_{12}, leading to caloric deprivation and vitamin B_{12} deficiency. However, because the bacteria produce folate, this deficiency is rare. The bacteria deconjugate bile salts, causing failure of micelle formation and subsequent fat malabsorption. Severe bacterial overgrowth also damages the intestinal mucosa. Fat malabsorption and mucosal damage can cause diarrhea.

Symptoms and Signs

Many patients are asymptomatic and present with only weight loss or nutrient deficiencies. The most frequent symptoms are abdominal discomfort, diarrhea, bloating, and excess flatulence. Some patients have significant diarrhea or steatorrhea.

Diagnosis

- ✓ ^{14}C-xylose breath test or quantitative culture of intestinal aspirate
- ✓ Sometimes upper GI series with small-bowel follow-through

Some clinicians advocate response to empiric antibiotic therapy as a diagnostic test. However, because bacterial overgrowth can mimic other malabsorptive disorders (eg, Crohn disease) and adverse effects of the antibiotics can worsen symptoms, establishing a definitive etiology is preferred.

The standard for diagnosis is quantitative culture of intestinal fluid aspirate showing a bacterial count $>10^5$/mL. This method, however, requires endoscopy. Breath tests, using substrates like glucose,lactulose, and xylose, are noninvasive and easy to do. The ^{14}C-xylose breath test seems to perform better than the other breath tests.

If the anatomic alterations are not due to previous surgery, an upper GI series with small-bowel follow-through should be done to identify predisposing anatomic lesions.

Treatment

- ✓ Oral antibiotics (various)
- ✓ Dietary modification

Treatment is with 10 to 14 days of oral antibiotics that cover both aerobic and anaerobic enteric bacteria. Empiric regimens include use of one of the following: tetracycline 250 mg qid,amoxicillin/clavulanic acid 250 to 500 mg tid, cephalexin250 mg qid,trimethoprim/sulfamethoxazole 160/800 mg bid, metronidazole250 to 500 mg tid or qid, orrifaximin 400 to 550 mg bid. Antibiotic treatment can be cyclic, if symptoms tend to recur, and changed based on culture and sensitivity. Changing antibiotic treatment may be difficult, however, due to coexistence of multiple bacteria.

Because bacteria metabolize primarily carbohydrates in the intestinal lumen rather than fats, a diet high in fat and low in carbohydrates and fiber is beneficial.

Underlying conditions and nutritional deficiencies (eg, vitamin B_{12}) should be corrected.

Key Points

- ✓ Anatomic alterations in stomach or intestines lead to GI stasis and thus bacterial overgrowth.
- ✓ Bacteria deconjugate bile salts, causing fat malabsorption.
- ✓ Diagnosis is made using the ^{14}C-xylose breath test or quantitative culture of intestinal aspirate.
- ✓ Oral antibiotics are used, and a high-fat, low-carbohydrate diet is followed.

Whipple disease

is a rare systemic illness caused by the bacterium Tropheryma whippelii. Main symptoms are arthritis, weight loss, abdominal pain, and diarrhea. Diagnosis is by small-bowel biopsy. Treatment is initially with ceftriaxone or penicillin followed by a minimum 1 yr of trimethoprim/sulfamethoxazole.

Whipple disease predominately affects white men aged 30 to 60. Although it affects many parts of the body (eg, heart, lung, brain, serous cavities, joints, eye, GI tract), the mucosa of the small bowel is almost always involved. Affected patients may have subtle defects of cell-mediated immunity that predispose to infection with T. whippelii. About 30% of patients have HLA-B27.

Symptoms and Signs

Clinical presentation varies depending on the organ systems affected. The four cardinal symptoms of Whipple disease are

- ✓ Arthralgia
- ✓ Diarrhea
- ✓ Abdominal pain
- ✓ Weight loss

Usually, the first symptoms are arthritis and fever. Intestinal symptoms (eg, watery diarrhea, steatorrhea, abdominal pain, anorexia, weight loss) usually manifest later, sometimes years after the initial complaint. Gross or occult intestinal bleeding may occur. Severe malabsorption may be present in patients diagnosed late in the clinical course. Other findings include increased skin pigmentation, anemia, lymphadenopathy, chronic cough, serositis, peripheral edema, and CNS symptoms.

Diagnosis

- ✓ Endoscopy with small-bowel biopsy

The diagnosis may be missed in patients without prominent GI symptoms. Whipple disease should be suspected in middle-aged white men who have arthritis and abdominal pain, diarrhea, weight loss, or other symptoms of malabsorption. Such patients should have upper endoscopy with small-bowel biopsy; the intestinal lesions are specific and diagnostic. The most severe and consistent changes are in the proximal small bowel. Light microscopy shows periodic acid-Schiff–positive macrophages that distort the villus architecture. Gram-positive, acid fast–negative bacilli (T. whippelii) are seen in the lamina propria and in the macrophages. Confirmation by electron microscopy is recommended.

Whipple disease should be differentiated from intestinal infection with Mycobacterium avium-intracellulare (MAI), which has similar histologic findings. However, MAI stains positive with acid fast. PCR testing may be useful for confirmation.

Treatment

- ✓ Antibiotics
- ✓ Late relapse a possibility

Untreated disease is progressive and fatal. Many antibiotics are curative (eg, tetracycline,trimethoprim/sulfamethoxazole, penicillin, cephalosporins). Treatment is initiated with ceftriaxone(2 g IV daily) or penicillin G(1.5 to 6 million units IV q 6 h). This regimen is followed by a long-term course of trimethoprim/sulfamethoxazole (160/800 mg po bid for 1 yr). Sulfa-allergic patients may substitute oral penicillin VK or ampicillin. Prompt clinical improvement occurs, with fever and joint pains resolving in a few days. Intestinal symptoms usually abate within 1 to 4 wk.

Some authorities do not recommend repeat small-bowel biopsies because macrophages may persist for years after treatment. However, others recommend repeat biopsy after 1 yr. In the latter approach, electron microscopy is needed to document bacilli (not just macrophages). Other authorities recommend using PCR testing for follow up instead of biopsy.

Relapses are common and may occur years later. If relapse is suspected, small-bowel biopsies or PCR testing should be done (regardless of affected organ systems) to determine presence of free bacilli.

Key Points

- ✓ Infection by the bacteria T. whippelii affects many organs, including the GI tract.
- ✓ Small bowel mucosal involvement causes malabsorption.
- ✓ Suspect Whipple disease in middle-aged white men who have arthritis and abdominal pain, diarrhea, weight loss, or other symptoms of malabsorption.

- ✓ Endoscopic small-bowel biopsy is necessary.
- ✓ Long-term antibiotic treatment is necessary, and relapses are common.

Equipment: study room, acknowledge with protocol and procedure of small intestine X-ray with contrast during visit to functional department (1st floor in University Clinic). Results of these investigations are provided to applicants during lesson.

Learning hours: 2 hours.

Plan of the lesson

I. Organizational moment (greetings, checking who is present on the lesson, announcing topic and goal of the lesson, motivating applicants to study the topic).

II. Control of basic knowledge (oral questioning, tests, checking of how clinical cases and workbooks are fulfilled).

2.1. Demands for applicants theoretical preparation

Applicants should know.

Didactic units list:

1. Definition. Etiology, pathogenesis of celiac disease.
2. Screening and risk factors.
3. Clinical manifestations.
4. Methods of diagnostics of celiac disease.
5. Differential diagnostics.
6. Treatment.
7. Prognosis.

Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Tests for self-control

1.Malabsorbtion is:
A. Absorbtion disturbance.+
B. Alimentary disturbance.
C. Splitting disturbance.
D. All of above.
E. None of above.
2. Chronic anemia is a clinical appearing and complication of what syndrome?
A. Maldigestion.
B. Malnutrition.
C. Malabsorbtion.
D. All of above. +
E. None of above.
3. The most precise method of small intestinum mucous evaluation is:
A. Upper endoscopy.
B. X-raying.
C. X-raying with contrast.
D. Videocapsule endoscopy. +
E. Colonoscopy.
4. Basic treatment of celiac disease is:
A. Severe gluten free diet.
B. Gluten free diet + prednison.

C. Gluten free diet + spasmolitic.
D. All of above.
E. Grounded medicament treatment every separate patient + gluten free diet. +
5.Changes of small intestinum mucous are characterized:
A. Complete atrophy of villi .
B. Atrophy of villi and cripts hyperplasy.
C. Lympho-plasmacyte infiltration.
D. Eosinophyle infiltration.
E. B + C. +
6. Malabsorbtion is caused by:
A. Celiac disease.
B. Chronic pancreatitis.
C. Cron's disease.
D. All of above. +
E. None of above.
7. Patient 48 y.o., complaints: periodic intensive pain n right hypochondrium with the irradiation to the back, nausea, frequent liquid stool, weight loss on 12 kg for 12 month. Objective: low nutrition, intensive pain in Dejarden's point. Liver +1 sm. Defecation 3-4 times per day with fatty mix. In urine: diastase – 16 U. What diagnosis is most likely?
A. Chronic pancreatitis. +
B. Chronic hepatitis.
C. Chronic enterocolitis.
D. Gluten enteropathy.
E. Autoimmune gastritis.
8. Patient 34 y.o., complaints: pain in ileosacral region from the right, frequent diarrhea with blood, arthralgias, increased body temperature. Abdomen is soft, painfull in ileocecal region. On X-ray – on relief of mucous revealed the contrast spots, ileocecal narrow crossing. What diagnosis is most likely?
A. Gluten enteropathy.
B. Cron's disease. +
C. Ulcer colitis.
E. Pseudomembranose colitis.
D. Tuberculosis ileitis.
9. The patient 14 y.o., complaints ongeneral weakness, weight loss. The condition worsened after taking a lot of wheat flakes. This happened from the childhood. Objective: low nutrition, delay in physical development. The reason of the disease in this case is:
A. Gluten enteropathy. +
B. Intestinal worm invasion.
C. Chronic pancreatitis.
D. Intestinal disbacteriosis.
E. Lactose deficit.
III. Formation of professional skills, abilities:

3.1. content of tasks (tasks, clinical situations, etc.)

Case history #1 A 46-year-old woman presents with fatigue and is found to have iron deficiency with anaemia. She has experienced intermittent episodes of mild diarrhoea for many years, previously diagnosed as irritable bowel syndrome and lactose intolerance. She has no current significant gastrointestinal symptoms such as diarrhoea, bloating, or abdominal pain. Examination reveals two oral aphthous ulcers and pallor. Abdominal examination is normal and results of faecal testing for occult blood are negative.

Case history #2 A 9-year-old boy presents with vomiting for 5 days. His sister, who has coeliac disease, has had similar symptoms. His growth has been normal and he has not experienced any other possible symptoms of coeliac disease, except for intermittent constipation. Immunoglobulin A-tissue transglutaminase titre is 5 times the upper limit of normal.

Task: Applicant should write diagnosis, plan of investigation, carry out differential diagnosis, prescribe treatment for these case histories.

3.2. recommendations (instructions) for performing tasks (professional algorithms, orientation maps for the formation of practical skills, etc.)

Professional algorithms.

X. Patient's examination.

During patient's examination students should keep such communicative skills:
1. Friendly face expression.
2. Kind voice tone.
3. Greetings, showing concern and respect about the patient.
4. Find out patient's complaints and anamnesis .
5. Explanation of investigation results.
6. Explanation of specific actions (hospitalization, carrying out investigations) which are planned to be performed in the future.
7. Finishing of the talk.

XI. Patient's examination and investigation algorithm.

1. It should be explained to patient which investigation will be held and indications for this investigation.
2. A doctor should receive patient's agreement on investigation.
3. A doctor should warn patient about possibilities of unpleasant feelings during investigation.
4. Results of investigation should be explained to a patient.
5. Immunoglobulin A-tissue transglutaminase (IgA-tTG) titre should be evaluated.
6. Endomysial antibody (EMA) is a more expensive alternative to IgA-tTG, with greater specificity but lower sensitivity, which may be used if IgA-tTG is unavailable.
7. Small intestinal biopsies should be obtained regardless of the IgA-tTG result in patients with a high clinical index of suspicion.
8. Paediatric patients with symptoms consistent with coeliac disease and a high IgA-tTG titre (above 10 times normal range for laboratory) may go on to have confirmatory EMA and human leukocyte antigen (HLA)-DQ2/-DQ8 testing. If both are positive, coeliac disease may be diagnosed without a small intestinal biopsy.
9. To diagnose coeliac disease, intra-epithelial lymphocytes should be increased and the villous-to-crypt ratio decreased.
10. Atrophy and scalloping of mucosal folds; nodularity and mosaic pattern of mucosa may be seen, but these findings are not sensitive for coeliac disease diagnosis will be revealed on endoscopy.

XII. Step-by-step algorithm of treatment.

1. A patient should informed be about necessity of the prescribed treatment.
2. Dosages, drugs intake regimens, duration of treatment, side effects of the prescribed therapy should be kindly explained to patient.
3. After diagnosis the patient should be referred to a dietician with specific training in coeliac disease and the gluten-free diet.
4. All patients with coeliac disease should be recommended to take calcium and vitamin D supplements.
5. Iron should only be given to individuals with iron deficiency.

6. Bone mineral density should be evaluated after approximately 1 year on a gluten-free diet to assess for osteopenia or osteoporosis.
7. Coeliac crisis is rare and presents with hypovolaemia, severe watery diarrhoea, acidosis, hypocalcaemia, and hypoalbuminaemia.
8. . In addition to rehydration and correction of electrolyte abnormalities, these few patients may benefit from a short course of systemic glucocorticoid therapy until the gluten-free diet takes effect.

3.3. requirements for applicants work results.
As a results of studying students must perform the following:
-possess skills of communication and clinical examination of a patient with celiac disease;
-collect data on patient complaints, medical history, life history;
-evaluate information about the diagnosis of celiac disease using a standard procedure, based on the results of laboratory, instrumental and morphological studies;
-determine the list of required clinical, laboratory and instrumental studies and evaluate their results;
- identify the leading clinical symptom or syndrome. Establish the most probable or syndrom diagnosis;
-assign laboratory and instrumental investigations for patient.
-carry out differential diagnosis ulcer disease;
-establish preliminary and clinical diagnosis;
- determine the principles of treatment, diet regimen for the patient.

3.4. control materials for the final stage of the lesson.

Work 1
1. Collection of complaints, anamnesis, examination of a patient with celiac disease.
2. Detection of clinical and instrumental symptoms.
3. Grouping symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data (clinical analysis of blood, urine, biochemical analysis of blood, immunological blood test, coprogramm, X-ray with barium, small intestinal biopsy, etc.).
6. Carrying out a differential diagnosis.
7. Formulation of the clinical diagnosis.
8. Write a prescription list for patients diagnosed with coeliac disease, which would include diet and prescribed drugs.
9. Determining of the disability degree.

Work 2.
Assignment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.
Work in the Internet, in the reading room of the department library with thematic literature.
The student fills in the protocol of the patient's examination. An example of the initial examination of the patient is attached.

The tests for self-control with standard answers.
1. A 51-year-old female patient complains of frequent defecation and liquid blood-streaked stools with mucus admixtures, diffuse pain in the inferolateral abdomen, 6 kg weight loss over the previous month. Objectively: body temperature - 37,4ºC, malnutrition, skin is pale and dry.

Abdomen is soft, sigmoid is painful and spasmodic, makes a rumbling sound. Liver is dense, painful, extends 3 cm below the costal margin. What is the most likely diagnosis?
A Non-specific ulcerative colitis
B Bacillary dysentery
C Sprue
D Intestinal enzymopathy
E Helminthic invasion
2. A 55 y.o. patient complains of distended abdomen and rumbling, increased winds evacuation, liquid foamy faeces with sour smell following the diary products consumption. What is the correct name of this syndrome?
A Syndrome of decayed dyspepsia
B Syndrome of fermentative dyspepsia
C Syndrome of fatty dyspepsia
D Dyskinesia syndrome
EMalabsorption syndrome

Standard answers: 1-A, 2-B.
IV. Summarizing, announcing the final grade, announcing the task for the next lesson.

Recommended resources:
- Basic literature source:
1. Celiac Disease Clinical Practice Guidelines 2019 by the European Society for the Study of *Coeliac Disease*(ESsCD)

Appendix 1

Example of the primary examination of the patient
Passport data: name and surname, age
Complaints:
severe weakness, significant weight loss, increased hair loss, bleeding gums, menstrual irregularities, pain in bones and muscles, diarrhea 5-10 times a day, bloating, rumbling.
Anamnesis morbid
Ill since childhood. Exacerbations after food intake containing gluten.
Anamnesis vitae
Living conditions are satisfactory. Botkin's disease, tuberculosis, sexually transmitted diseases, malaria denies.
Professional anamnesis: not burdened.
Hereditary history is not burdened.
Pave not been in contact with infectious patients for the last 3 days. He has not left the country in the last 3 years.
***Hereditary history**: not burdened*
Neurological history
At the time of examination signs of focal neurological symptoms were not detected.
***Allergic history**: not burdened*
Epidemiology
Tuberculosis, malaria, viral hepatitis, Botkin's disease, veneral disease, HIV, AIDS, pediculosis – denies.
***Oncoanamnesis**: denies.*
***Insurance anamnesis**: There is no need to issue a seak leave, for the last 12 months a seak leave document has not been issued in this regard.*
***Postponed operations**: denies.*
***Bad habits**: denies.*

Examination of organ systems:
GENERAL Condition: satisfactory
CONSCIOUSNESS: clear
Body shape: hypostenic
Fatness: low nutrition
POSITION OF THE PATIENT: active
BODY TEMPERATURE: 36.6 C. Signs of alcohol intoxication - no
SKIN: Skin of normal color, clean. Tissue turgor is normal. Skin pigmentation: depigmentation - no. Rash: no; other changes in the skin: no.
Visible mucous membranes: Normal color
LYMPH NODES: not enlarged
THYROID GLAND: no pathology
Oncological examination was performed, no visual forms of oncopathology were detected
Cardiovascular system:
PERCUSSION OF THE HEART: the limits of relative cardiac dullness: right on the right edge of the sternum, upper -III rib on the left parasternalis line, left – on the line mediaclavicularis in the V intercostal space
HEART activity: rhythmic, heart rate - 74 per 1 min. Pulse 74 in 1 min. Heart tones: muffled
HEART MURMURS: no
EDEMA: no
BP 125 / 85 mm Hg
EXAMINATION OF ARTERIES: no pathology
VEIN STUDY: no pathology
RESPIRATORY SYSTEM:
BREATHING: no dyspnea at rest, RR 16 in 1 min.
Sputum: no
CHEST: cylindrical, not deformed. Intercostal spaces: NOT smoothed. Participation of additional muscles: no, RR – 16 in 1 min. SpO2 = 98%
Percussion over the lungs: clear lung sound.
PULMONARY AUSCULTATION: vesicular breathing over both lungs. Pleural friction noise - no
DIGESTIVE SYSTEM:
TONGUE: wet; papillae smoothed
Tonsils: not enlarged
STOMACH: moderately swollen, more around the navel, participates in the act of breathing. No hernia. Pulsation in the epigastrium - no. There is no dilation of the subcutaneous veins
Palpation: moderately painful in the paraumbilicalus region
Pathological symptoms: not detected
Liver: not enlarged
Gallbladder: not palpable
Pancreas: painless
Spleen: not palpable,
PERCUTIONAL SOUND OVER THE ABDOMINAL CAVITY: unchanged,
FECES: normal, no pathological impurities
URINARY SYSTEM:
Palpation of the kidneys: not palpable
Pasternatsky's symptom is negative on both sides.
Urination: free, painless, frequency per day: 3-4 times.
Urinary incontinence: no.
SENSES:
SIGHT: not violated (OU). There is no other pathology
HEARING: normal, no deafness, pain: no. Tinnitus: no.
Musculoskeletal system:

Pathology of the musculoskeletal system was not detected

On the basis of complaints, anamnesis, objective examination, it is possible to make a preliminary diagnosis:

Coeliac disease

Plan of investigation

general blood test, general urine test, glycemia level (8.00, 13.00, 17.00, 21.00).

Biochemistry: liver tests, glucose, transaminases, protein, lipid spectrum, coagulogram, amylase, AF, LDG, GGT, CPK, serum iron, potassium, calcium, CRP, vitamins B12, folic acid, immunoglobulin A-tissue transglutaminase and endomyosial antibody in serum.

Consultation with gastroenterologist.

Treatment plan

Normalization of lifestyle

Gluten-free diet

Drug therapy:

Vitamins (B12, folic acid), microelements (iron, calcium) at need.

Appendix 2

Tests of basic knowledge level in KROK format
Theme 21. Coeliac disease and other enteropathy

1. A 51-year-old female patient complains of frequent defecation and liquid blood-streaked stools with mucus admixtures, diffuse pain in the inferolateral abdomen, 6 kg weight loss over the previous month. Objectively: body temperature - 37,4ºC, malnutrition, skin is pale and dry. Abdomen is soft, sigmoid is painful and spasmodic, makes a rumbling sound. Liver is dense, painful, extends 3 cm below the costal margin. What is the most likely diagnosis?
A. Non-specific ulcerative colitis
B. Bacillary dysentery
C. Sprue
D. Intestinal enzymopathy
E. Helminthic invasion
2. A 55 y.o. patient complains of distended abdomen and rumbling, increased winds evacuation, liquid foamy faeces with sour smell following the diary products consumption. What is the correct name of this syndrome?
A. Syndrome of decayed dyspepsia
B. Syndrome of fermentative dyspepsia
C. Syndrome of fatty dyspepsia
D. Dyskinesia syndrome
E. Malabsorption syndrome
3. Chronic anemia is a clinical appearing and complication of what syndrome?
A. Maldigestion.
B. Malnutrition.
C. Malabsorbtion.
D. All of above.
E. None of above.
4. The most precise method of small intestinum mucous evaluation is:
A. Upper endoscopy.
B. X-raying.
C. X-raying with contrast.
D. Videocapsule endoscopy.

E. Colonoscopy.
5. Basic treatment of celiac disease is:
A. Severe gluten free diet.
B. Gluten free diet + prednison.
C. Gluten free diet + spasmolitic.
D. All of above.
E. Grounded medicament treatment every separate patient + gluten free diet. +
6.Changes of small intestinum mucous are characterized:
A. Complete atrophy of villi .
B. Atrophy of villi and cripts hyperplasy.
C. Lympho-plasmacyte infiltration.
D. Eosinophyle infiltration.
E. B + C.
7. Malabsorbtion is caused by:
A. Celiac disease.
B. Chronic pancreatitis.
C. Cron's disease.
D. All of above.
E. None of above.
8. Patient 48 y.o., complaints: periodic intensive pain n right hypochondrium with the irradiation to the back, nausea, frequent liquid stool, weight loss on 12 kg for 12 month. Objective: low nutrition, intensive pain in Dejarden's point. Liver +1 sm. Defecation 3-4 times per day with fatty mix. In urine: diastase – 16 U. What diagnosis is most likely?
A. Chronic pancreatitis.
B. Chronic hepatitis.
C. Chronic enterocolitis.
D. Gluten enteropathy.
E. Autoimmune gastritis.
9. Patient 34 y.o., complaints: pain in ileosacral region from the right, frequent diarrhea with blood, arthralgias, increased body temperature. Abdomen is soft, painfull in ileocecal region. On X-ray – on relief of mucous revealed the contrast spots, ileocecal narrow crossing. What diagnosis is most likely?
A. Gluten enteropathy.
B. Cron's disease.
C. Ulcer colitis.
E. Pseudomembranose colitis.
D. Tuberculosis ileitis.
10. The patient 14 y.o., complaints ongeneral weakness, weight loss. The condition worsened after taking a lot of wheat flakes. This happened from the childhood. Objective: low nutrition, delay in physical development. The reason of the disease in this case is:
A. Gluten enteropathy.
B. Intestinal worm invasion.
C. Chronic pancreatitis.
D. Intestinal disbacteriosis.
E. Lactose deficit.

Practical lesson #22
1. Theme: Chronic colon diseases: IBS and nonspecific colitis.

2. Goal:
To study:
- Etiology, pathogenesis of IBS, ulcerative colitis, Crohn's disease, classification, clinic, complications, diagnosis and treatment.
- General, dietary and pharmacological recommendations.
- Classification and pharmacological peculiarity of drugs, which are used in chronic colon diseases.

3 **Basic concepts.** IBS: definition, aetiology. Diagnosis and differential diagnostics. Treatment. Ulcerative colitis and Crohn's disease: definition, aetiology, pathophysiology. Classification. Diagnostics, differential diagnostics. Treatment. Complications. Prognosis.

Irritable bowel syndrome (IBS)
is characterized by recurrent abdominal discomfort or pain that is accompanied by at least two of the following: relief by defecation, change in frequency of stool, or change in consistency of stool. The cause is unknown, and the pathophysiology is incompletely understood. Diagnosis is clinical. Treatment is symptomatic, consisting of dietary management and drugs, including anticholinergics and agents active at serotonin receptors.

Etiology
The cause of IBS is unknown. No anatomic cause can be found on laboratory tests, x-rays, and biopsies. Emotional factors, diet, drugs, or hormones may precipitate or aggravate GI symptoms. Historically, the disorder was often considered as purely psychosomatic. Although psychosocial factors are involved, IBS is better understood as a combination of psychosocial and physiologic factors.

Psychosocial factors:
Psychologic distress is common among patients with IBS, especially in those who seek medical care. Some patients have anxiety disorders, depression, or a somatization disorder. Sleep disturbances also coexist. However, stress and emotional conflict do not always coincide with symptom onset and recurrence. Some patients with IBS seem to have a learned aberrant illness behavior (ie, they express emotional conflict as a GI complaint, usually abdominal pain). The physician evaluating patients with IBS, particularly those with refractory symptoms, should investigate for unresolved psychologic issues, including the possibility of sexual or physical abuse. Psychosocial factors also affect the outcome in IBS.

Physiologic factors:
A variety of physiologic factors seem to be involved in IBS symptoms. These factors include altered motility, visceral hyperalgesia, and various genetic and environmental factors.
Visceral hyperalgesia refers to hypersensitivity to normal amounts of intraluminal distention and heightened perception of pain in the presence of normal quantities of intestinal gas; it may result from remodeling of neural pathways in the brain-gut axis. Some patients (perhaps 1 in 7) have reported their IBS symptoms began after an episode of acute gastroenteritis (termed postinfectious IBS). A subset of patients with IBS has autonomic dysfunctions. However, many patients have no demonstrable physiologic abnormalities, and, even in those that do, the abnormalities may not correlate with symptoms.
Constipation may be explained by slower colonic transit, and diarrhea may be explained by faster colonic transit. Some patients with constipation have fewer colonic high amplitude-propagated contractions, which propel colonic contents over several segments. Conversely, excess sigmoid motor activity may retard transit in functional constipation.
Postprandial abdominal discomfort may be attributed to an exaggerated gastro-colonic reflex (the colonic contractile response to a meal), the presence of colonic high amplitude-propagated contractions, increased intestinal sensitivity (visceral hyperalgesia), or a combination of these

factors. Fat ingestion may increase intestinal permeability and exaggerate hypersensitivity. Ingestion of food high in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (collectively called FODMAPs) are poorly absorbed in the small intestine and may increase colonic motility and secretion.

Hormonal fluctuations affect bowel functions in women. Rectal sensitivity is increased during menses but not during other phases of the menstrual cycle. The effects of sex steroids on GI transit are subtle. The role of small-bowel bacterial overgrowth in IBS is controversial.

Symptoms and Signs

IBS tends to begin in adolescence and the 20s, causing bouts of symptoms that recur at irregular periods. Onset in late adult life is less common but not rare. Symptoms rarely rouse the sleeping patient. Symptoms are often triggered by food, particularly fats, or by stress.

Patients have abdominal discomfort, which varies considerably but is often located in the lower abdomen, steady or cramping in nature, and relieved by defecation. In addition, abdominal discomfort is temporally associated with alterations in stool frequency (increased in diarrhea-predominant IBS and decreased in constipation-predominant IBS) and consistency (ie, loose or lumpy and hard). Pain or discomfort related to defecation is likely to be of bowel origin; that associated with exercise, movement, urination, or menstruation usually has a different cause. Although bowel patterns are relatively consistent in most patients, it is not unusual for patients to alternate between constipation and diarrhea. Patients may also have symptoms of abnormal stool passage (straining, urgency, or feeling of incomplete evacuation), pass mucus, or complain of bloating or abdominal distention. Many patients also have symptoms of dyspepsia. Extra-intestinal symptoms (eg, fatigue, fibromyalgia, sleep disturbances, chronic headaches) are common.

Diagnosis

- ✓ Clinical evaluation, based on Rome criteria
- ✓ Screening for organic causes with basic laboratory tests and sigmoidoscopy or colonoscopy
- ✓ Other tests for patients with red flag findings (rectal blood, weight loss, fever)

Diagnosis is based on characteristic bowel patterns, time and character of pain, and exclusion of other disease processes through physical examination and routine diagnostic tests. Diagnostic testing should be more intensive when the following red flags are present either at initial presentation or at any time after diagnosis: older age, fever, weight loss, rectal bleeding, vomiting. Because patients with IBS can develop organic conditions, testing for other conditions should also be considered in patients who develop alarm symptoms or markedly different symptoms during the course of IBS. Common illnesses that may be confused with IBS include lactose intolerance, drug-induced diarrhea, post-cholecystectomy diarrhea, laxative abuse, parasitic diseases (eg, giardiasis), eosinophilic gastritis or enteritis, microscopic colitis, small-bowel bacterial overgrowth, celiac disease, and early inflammatory bowel disease. However, uninflamed colonic diverticula do not cause symptoms, and their presence should not be considered explanatory.

The bimodal age distribution of patients with inflammatory bowel disease makes it imperative to evaluate both younger and older patients. In patients > 60 with acute symptoms, ischemic colitis should be considered. Patients with constipation and no anatomic lesion should be evaluated for hypothyroidism and hyperparathyroidism. If the patient's symptoms suggest malabsorption, tropical sprue, celiac disease, and Whipple disease must be considered. Defecatory disorders should be considered as a cause of constipation in patients who report symptoms of difficult defecation. Rare causes of diarrhea include hyperthyroidism, medullary cancer of the thyroid, or carcinoid syndrome, gastrinoma, and vipoma. However, secretory diarrhea caused by vasoactive intestinal peptide (VIP),calcitonin, or gastrin is typically accompanied by stool volumes > 1000 mL daily.

History:

Particular attention should be given to the character of the pain, bowel habits, familial interrelationships, and drug and dietary histories. Equally important are the patient's overall emotional state, interpretation of personal problems, and quality of life. The quality of the patient-physician interaction is key to diagnostic and therapeutic efficacy.

The **Rome criteria** are standardized symptom-based criteria for diagnosing IBS. The Rome criteria require the presence of abdominal pain or discomfort for at least 3 days/mo in the last 3 mo along with≥ 2 of the following:

- ✓ Improvement with defecation
- ✓ Onset (of each episode of discomfort) associated with a change in frequency of defecation
- ✓ Change in consistency of stool

Physical examination:

Patients generally appear to be healthy. Palpation of the abdomen may reveal tenderness, particularly in the left lower quadrant, at times associated with a palpable, tender sigmoid. A digital rectal examination, including a test for occult blood, should be done on all patients. In women, a pelvic examination helps rule out ovarian tumors and cysts or endometriosis, which may mimic IBS.

Testing:

The diagnosis of IBS can reasonably be made using the Rome criteria as long as patients have no red flag findings, such as rectal bleeding, weight loss, and fever, or other findings that might suggest another etiology. Many patients with IBS are overtested; however, CBC, biochemical profile (including liver tests), ESR, stool examination for ova and parasites (in patients with diarrhea predominance), thyroid-stimulating hormone and Ca for patients with constipation, and flexible sigmoidoscopy or colonoscopy should be done. During flexible fiberoptic proctosigmoidoscopy, introduction of the instrument and air insufflation frequently trigger bowel spasm and pain. The mucosal and vascular patterns in IBS usually appear normal. Colonoscopy is preferred for patients > 50 with a change in bowel habits, particularly those with no previous IBS symptoms, to exclude colonic polyps and tumors. In patients with chronic diarrhea, particularly older women, mucosal biopsy can rule out possible microscopic colitis.

Additional studies (such as ultrasonography, CT, barium enema x-ray, upper GI esophagogastroduodenoscopy, and small-bowel x-rays) should be undertaken only when there are other objective abnormalities. Fecal fat excretion should be measured when there is a concern about steatorrhea. Testing for celiac disease and small-bowel x-rays are recommended when malabsorption is suspected. Testing for carbohydrate intolerance or small-bowel bacterial overgrowth should be considered in appropriate circumstances.

Intercurrent disease:

Patients with IBS may subsequently develop additional GI disorders, and the clinician must not summarily dismiss their complaints. Changes in symptoms (eg, in the location, type, or intensity of pain; in bowel habits; in constipation and diarrhea) and new symptoms or complaints (eg, nocturnal diarrhea) may signal another disease process. Other symptoms that require investigation include fresh blood in the stool, weight loss, very severe abdominal pain or unusual abdominal distention, steatorrhea or noticeably foul-smelling stools, fever or chills, persistent vomiting, hematemesis, symptoms that wake the patient from sleep (eg, pain, the urge to defecate), and a steady progressive worsening of symptoms. Patients > 40 are more likely than younger patients to develop an intercurrent physiologic illness.

Treatment

- ✓ Support and understanding
- ✓ Normal diet, avoiding gas-producing and diarrhea-producing foods
- ✓ Increased fiber intake for constipation
- ✓ Loperamidefor diarrhea
- ✓ Possibly tricyclic antidepressants

Therapy is directed at specific symptoms. An effective therapeutic relationship is essential for effectively managing IBS. Patients should be invited to express not only their symptoms but also their understanding of their symptoms and the reasons prompting a visit to the health care practitioner (eg, fear of serious disease). Patients should be educated about the disorder (eg, normal bowel physiology and the bowel's hypersensitivity to stress and food) and reassured, after

appropriate tests, about the absence of a serious or life-threatening disease. Appropriate therapeutic goals (eg, expectations regarding the normal course or variability in symptoms, adverse effects of drugs, the appropriate and available working relationship between the physician and the patient) should be established. Finally, patients can benefit by being actively involved in the management of their condition. When successful, this can enhance the patient's motivation to adhere to treatment, foster a more positive physician-patient relationship, and mobilize the coping resources of even the most chronically passive patients. Psychologic stress, anxiety, or mood disorders should be identified, evaluated, and treated. Regular physical activity helps relieve stress and assists in bowel function, particularly in patients with constipation.

Diet:

In general, a normal diet can be followed. Meals should not be overly large, and eating should be slow and paced. Patients with abdominal distention and increased flatulence may benefit from reducing or eliminating beans, cabbage, and other foods containing fermentable carbohydrates. Reduced intake of sweeteners (eg, sorbitol, mannitol, fructose), which are constituents of natural and processed foods (eg, apple and grape juice, bananas, nuts, and raisins), may alleviate flatulence, bloating, and diarrhea. Patients with evidence of lactose intolerance should reduce their intake of milk and dairy products. A low-fat diet may reduce postprandial abdominal symptoms.

Dietary fiber supplements may soften stool and improve the ease of evacuation. A bland bulk-producing agent may be used (eg, raw bran, starting with 15 mL [1 tbsp] with each meal, supplemented with increased fluid intake). Alternatively, psyllium hydrophilic mucilloid with two glasses of water may be used. However, excessive use of fiber can lead to bloating and diarrhea, so fiber doses must be individualized. Occasionally, flatulence may be reduced by switching to a synthetic fiber preparation (eg, methylcellulose).

Drug therapy:

Drug therapy is directed toward the dominant symptoms. Anticholinergic drugs (eg,hyoscyamine0.125 mg po 30 to 60 min before meals) may be used for their antispasmodic effects.

Serotonin receptor modulation may be of benefit. Tegaserod, a 5HT4 agonist, stimulates motility and alleviates constipation. In 2007, tegaserod was withdrawn from the market because, in clinical trials, it slightly increased the incidence of cardiovascular ischemic events (ie, MI, unstable angina pectoris, stroke) compared with placebo. Tegaserodhas since been reintroduced under a restricted program. The chloride channel activator lubiprostone and the guanylate cyclase C agonist linaclotide may help patients with constipation.

In patients with diarrhea, oral diphenoxylate 2.5 to 5 mg or loperamide2 to 4 mg may be given before meals. The dose of loperamide should be titrated upward to reduce diarrhea while avoiding constipation. For many patients, tricyclic antidepressants (TCAs) help relieve symptoms of diarrhea, abdominal pain, and bloating. These drugs are thought to reduce pain by down-regulating the activity of spinal cord and cortical afferent pathways arriving from the intestine. Secondary amine TCAs (eg. nortriptyline, desipramine) are often better tolerated than parent tertiary amines (eg,amitriptyline, imipramine, doxepin) because of fewer anticholinergic, sedating antihistaminic, and α-adrenergic adverse effects. Treatment should begin with a very low dose of a TCA (eg,desipramine10 to 25 mg once/day at bedtime), increasing as necessary and tolerated up to about 100 to 150 mg once/day. SSRIs are also useful, particularly for patients with anxiety or an affective disorder, but may exacerbate diarrhea. 5HT3 antagonists (eg, alosetron) may benefit female patients with severe diarrhea refractory to other drugs. Because alosetron is associated with ischemic colitis, its use is restricted.

Preliminary data suggest that certain probiotics (eg, Bifidobacterium infantis) alleviate IBS symptoms, particularly bloating. The beneficial effects of probiotics are not generic to the entire species but specific to certain strains. Certain aromatic oils (carminatives) can relax smooth muscle and relieve pain caused by cramps in some patients. Peppermint oil is the most commonly used agent in this class.

Psychologic therapies:
Cognitive-behavioral therapy, standard psychotherapy, and hypnotherapy may help some IBS patients.

Key Points

- IBS is recurrent abdominal discomfort or pain accompanied by ≥ 2 of the following: relief by defecation, change in frequency of stool (diarrhea or constipation), or change in consistency of stool.

- Etiology is unclear but appears to involve both psychosocial and physiologic factors.

- Exclude more dangerous diseases by testing, particularly in patients with red flag findings, such as older age, fever, weight loss, rectal bleeding, or vomiting.

- Common illnesses that may be confused with IBS include lactose intolerance, drug-induced diarrhea, post-cholecystectomy diarrhea, laxative abuse, parasitic diseases, eosinophilic gastritis or enteritis, microscopic colitis, small-bowel bacterial overgrowth, celiac disease, and early inflammatory bowel disease.

- Typical testing includes CBC, biochemical profile (including liver tests), ESR, stool examination for ova and parasites (in patients with diarrhea predominance), thyroid-stimulating hormone and Ca for patients with constipation, and flexible sigmoidoscopy or colonoscopy.

- A supportive, understanding, and therapeutic relationship is essential; direct drug therapy toward the dominant symptoms.

Inflammatory bowel disease (IBD),
which includes Crohn disease and ulcerative colitis (UC), is a relapsing and remitting condition characterized by chronic inflammation at various sites in the GI tract, which results in diarrhea and abdominal pain.

Inflammation results from a cell-mediated immune response in the GI mucosa. The precise etiology is unknown, but evidence suggests that the normal intestinal flora trigger an abnormal immune reaction in patients with a multifactorial genetic predisposition (perhaps involving abnormal epithelial barriers and mucosal immune defenses). No specific environmental, dietary, or infectious causes have been identified. The immune reaction involves the release of inflammatory mediators, including cytokines, interleukins, and TNF.

Although Crohn disease and UC are similar, they can be distinguished in most cases. About 10% of colitis cases are considered indeterminate. The term colitis applies only to inflammatory disease of the colon (eg, ulcerative, granulomatous, ischemic, radiation-induced, infectious). Spastic (mucous) colitis is a misnomer sometimes applied to a functional disorder, irritable bowel syndrome

Differentiating Crohn Disease and Ulcerative Colitis

Crohn Disease	Ulcerative Colitis
Small bowel is involved in 80% of cases.	Disease is confined to the colon.
Rectosigmoid is often spared; colonic involvement is usually right-sided.	Rectosigmoid is invariably involved; colonic involvement is usually left-sided.
Gross rectal bleeding is rare, except in 75–85% of cases of Crohn colitis.	Gross rectal bleeding is always present.
Fistula, mass, and abscess development is common.	Fistulas do not occur.
Perianal lesions are significant in 25–35% of cases.	Significant perianal lesions never occur.
On x-ray, bowel wall is affected asymmetrically and segmentally, with skip	Bowel wall is affected symmetrically and uninterruptedly from rectum proximally.

areas between diseased segments.	
Endoscopic appearance is patchy, with discrete ulcerations separated by segments of normal-appearing mucosa.	Inflammation is uniform and diffuse.
Microscopic inflammation and fissuring extend transmurally; lesions are often highly focal in distribution.	Inflammation is confined to mucosa except in severe cases.
Epithelioid (sarcoid-like) granulomas are detected in bowel wall or lymph nodes in 25–50% of cases (pathognomonic).	Typical epithelioid granulomas do not occur.

Epidemiology:

IBD affects people of all ages but usually begins before age 30, with peak incidence from 14 to 24. IBD may have a second smaller peak between ages 50 and 70; however, this later peak may include some cases of ischemic colitis.

IBD is most common among people of Northern European and Anglo-Saxon origin and is 2 to 4 times more common among Ashkenazi Jews than non-Jewish whites. The incidence is lower in central and southern Europe and lower still in South America, Asia, and Africa. However, the incidence is increasing among blacks and Latin Americans living in North America. Both sexes are equally affected. First-degree relatives of patients with IBD have a 4- to 20-fold increased risk; their absolute risk may be as high as 7%. Familial tendency is much higher in Crohn disease than in UC. Several gene mutations conferring a higher risk of Crohn disease (and some possibly related to UC) have been identified.

Cigarette smoking seems to contribute to development or exacerbation of Crohn disease but decreases risk of UC. Appendectomy done to treat appendicitis also appears to lower the risk of UC. NSAIDs may exacerbate IBD. Oral contraceptives may increase the risk of Crohn disease, andisotretinoinmay increase the risk of UC. Some data suggest that perinatal illness and the use of antibiotics in childhood may be associated with an increased risk of IBD.

Extraintestinal Manifestations

Crohn disease and UC both affect organs other than the intestines. Most extraintestinal manifestations are more common in UC and Crohn colitis than in Crohn disease limited to the small bowel. Extraintestinal manifestations are categorized in 3 ways:

1.Disorders that usually parallel (ie, wax and wane with) IBD flare-ups: These disorders include peripheral arthritis, episcleritis, aphthous stomatitis, erythema nodosum, and pyoderma gangrenosum. Arthritis tends to involve large joints and be migratory and transient. One or more of these parallel disorders develops in more than one third of patients hospitalized with IBD.

2.Disorders that are clearly associated with IBD but appear independently of IBD activity: These disorders include ankylosing spondylitis, sacroiliitis, uveitis, and primary sclerosing cholangitis. Ankylosing spondylitis occurs more commonly in IBD patients with the HLA-B27 antigen. Most patients with spinal or sacroiliac involvement have evidence of uveitis and vice versa. Primary sclerosing cholangitis, which is a risk factor for cancer of the biliary tract, is strongly associated with UC or Crohn colitis. Cholangitis may appear before or concurrently with the bowel disease or even 20 yr after colectomy. Liver disease (eg, fatty liver, autoimmune hepatitis, pericholangitis, cirrhosis) occurs in 3 to 5% of patients, although minor abnormalities in liver function tests are more common. Some of these conditions (eg, primary sclerosing cholangitis) may precede IBD by many years and, when diagnosed, should prompt an evaluation for IBD.

3.Disorders that are consequences of disrupted bowel physiology: These disorders occur mainly in severe Crohn disease of the small bowel. Malabsorption may result from extensive ileal resection and cause deficiencies of fat-soluble vitamins, vitamin B_{12}, or minerals, resulting in anemia, hypocalcemia, hypomagnesemia, clotting disorders, and bone demineralization. In children, malabsorption retards growth and development. Other disorders include kidney stones from

excessive dietary oxalate absorption, hydroureter and hydronephrosis from ureteral compression by the intestinal inflammatory process, gallstones from impaired ileal reabsorption of bile salts, and amyloidosis secondary to long-standing inflammatory and suppurative disease.
Thromboembolic disease may occur as a result of multiple factors in all 3 categories.

Treatment

- ✓ Supportive care
- ✓ 5-Aminosalicylic acid
- ✓ Corticosteroids
- ✓ Immunomodulating drugs
- ✓ Anticytokine drugs
- ✓ Sometimes antibiotics (eg, metronidazoly, ciprofloxacin) and probiotics

Several classes of drugs are helpful for IBD. Details of their selection and use are discussed under each disorder.

5-Aminosalicylic acid (5-ASA, mesalamine):

5-ASA blocks production of prostaglandins and leukotrienes and has other beneficial effects on the inflammatory cascade. Because 5-ASA is active only intraluminally and is rapidly absorbed by the proximal small bowel, it must be formulated for delayed absorption when given orally. Sulfasalazine, the original agent in this class, delays absorption by complexing 5-ASA with a sulfa moiety, sulfapyridine. The complex is cleaved by bacterial flora in the lower ileum and colon, releasing the 5-ASA. The sulfa moiety, however, causes numerous adverse effects (eg, nausea, dyspepsia, headache), interferes with folate (folic acid) absorption, and occasionally causes serious adverse reactions (eg, hemolytic anemia or agranulocytosis and, rarely, hepatitis or pneumonitis). Reversible decreases in sperm count and motility occur in up to 80% of men. If used, sulfasalazineshould be given with food, initially in a low dosage (eg, 0.5 g po bid) and gradually increased over several days to 1 to 2 g bid to tid. Patients should take daily folate supplements (1 mg po) and have CBC and liver tests every 6 to 12 mo. Acute interstitial nephritis secondary to mesalamineoccurs rarely; periodic monitoring of renal function is advisable because most cases are reversible if recognized early.

Newer drugs that complex 5-ASA with other vehicles seem almost equally effective but have fewer adverse effects. Olsalazine (a 5-ASA dimer) and balsalazide (5-ASA conjugated to an inactive compound) are cleaved by bacterial azoreductases (as is sulfasalazine). These drugs are activated mainly in the colon and are less effective for proximal small-bowel disease. Olsalazine dosage is 500 to 1500 mg po bid, and balsalazideis 2.25 g po tid. Olsalazine sometimes causes diarrhea, especially in patients with pancolitis. This problem is minimized by gradual escalation of dose and administration with meals.

Other forms of 5-ASA use delayed-release coatings. Asacol (typical dose 800 to 1200 mg po tid) is 5-ASA coated with an acrylic polymer whose pH solubility delays release of the drug until entry into the distal ileum and colon. Pentasa (1 g po qid) is 5-ASA encapsulated in ethylcellulose microgranules that release 35% of the drug in the small bowel. Two once/day formulations of mesalamine(Lialda, Apriso) are available; this less frequent dosing may improve adherence.

5-ASA is also available as a suppository (500 or 1000 mg at bedtime or bid) or enema (4 g at bedtime or bid) for proctitis and left-sided colon disease. These rectal preparations are effective for both acute treatment and long-term maintenance in proctitis and left-sided colon disease and they have incremental benefit in combination with oral 5-ASA.

Corticosteroids:

Corticosteroids are useful for acute flare-ups of most forms of IBD when 5-ASA compounds are inadequate. However, corticosteroids are not appropriate for maintenance. IVhydrocortisone300 mg/day or methylprednisolone60 to 80 mg/day by continuous drip or in divided doses (eg, 30 to 40 mg po bid) is used for severe disease; oral prednisoneor prednisolone40 to 60 mg once/day may be used for moderate disease. Treatment is continued until symptoms remit (usually 7 to 28 days) and then tapered by 5 to 10 mg weekly to 20 mg once/day. Treatment is then further tapered by 2.5 to 5

mg weekly while instituting maintenance therapy with 5-ASA or immunomodulators. Adverse effects of short-term corticosteroids in high doses include hyperglycemia, hypertension, insomnia, hyperactivity, and acute psychotic episodes.

Hydrocortisone enemas or foam may be used for proctitis and left-sided colon disease; as an enema, 100 mg in 60 mL of isotonic solution is given once/day or bid. The enema should be retained in the bowel as long as possible; instillation at night, with the patient lying on the left side with hips elevated, may prolong retention and extend distribution. Treatment, if effective, should be continued daily for about 2 to 4 wk, then every other day for 1 to 2 wk, and then gradually discontinued over 1 to 2 wk.

Budesonide is a corticosteroid with a high (> 90%) first-pass liver metabolism; thus, oral administration may have a significant effect on GI tract disease but minimal adrenal suppression. Oralbudesonide has fewer adverse effects than prednisolonebut is not as rapidly effective and is typically used for less severe disease. Budesonidemay be effective in maintaining remission for 3 to 6 mo but has not yet proved effective for long-term maintenance. Dosage is 9 mg once/day. It is also available outside the US as an enema.

Immunomodulating drugs:

Azathioprineand its metabolite 6-mercaptopurineinhibit T-cell function. They are effective long-term and may diminish corticosteroid requirements and maintain remission for years. These drugs often require 1 to 3 mo to produce clinical benefits, so corticosteroids cannot be withdrawn until at least the 2nd month. Dosage of azathioprineis usually 2.5 to 3.0 mg/kg po once/day and 6-mercaptopurineis 1.5 to 2.5 mg/kg po once/day but varies depending on individual metabolism. Signs of bone marrow suppression must be monitored with regular WBC count (biweekly for 1 mo, then every 1 to 2 mo). Pancreatitis or high fever occurs in about 3 to 5% of patients; either is an absolute contraindication to rechallenge. Hepatotoxicity is rarer and can be screened by blood tests every 6 to 12 mo. Newly available blood tests that measure the activity of one of the enzymes that metabolize azathioprine and 6-mercaptopurine and that directly measure metabolite levels may sometimes be helpful in ensuring safe and effective drug dosages.Methotrexate15 to 25 mg po or sc weekly is of benefit to many patients with corticosteroid-refractory or corticosteroid-dependent Crohn disease, even those who have not responded toazathioprineor 6-mercaptopurine. Adverse effects include nausea, vomiting, and asymptomatic liver function test abnormalities. Folate 1 mg po once/day may diminish some of the adverse effects. Women taking methotrexateshould be using at least one form of birth control. Additionally, women and perhaps men should stop methotrexatefor at least 3 mo before trying to conceive. Monthly CBCs and liver function tests with albumin should be done for the first 3 mo of therapy then every 8 to 12 wk during therapy. Alcohol use, obesity, diabetes, and possibly psoriasis are risk factors for hepatotoxicity. Preferably, patients with these conditions should not be treated with methotrexate. Pretreatment liver biopsies are not recommended; liver biopsies are done if the results of 6 of 12 tests done in a 1-yr period show elevated levels of AST. Myelosuppression, pulmonary toxicity, and nephrotoxicity can also occur with methotrexatetherapy.

Cyclosporine, which blocks lymphocyte activation, may benefit patients with severe UC unresponsive to corticosteroids and who may otherwise require colectomy. Its only well-documented use in Crohn disease is for patients with refractory fistulas or pyoderma. Initial dose is 4 mg/kg IV in continuous infusion over 24 h; responders are converted to an oral dose of 6 to 8 mg/kg once/day with early introduction of azathioprineor 6-mercaptopurine. Long-term use (> 6 mo) is contraindicated by multiple adverse effects (eg, renal toxicity, seizures, opportunistic infections, hypertension, neuropathy). Generally, patients are not offered cyclosporineunless there is a reason to avoid the safer curative option of colectomy. If the drug is used, trough blood levels should be kept between 200 to 400 ng/mL and *Pneumocystis jirovecii* prophylaxis should be considered during the period of concomitant corticosteroid, cyclosporine, and antimetabolite treatment. Tacrolimus, an immunosuppressant also used in transplant patients, seems as effective as cyclosporine.

Anticytokine drugs:

Infliximab, certolizumab, and adalimumabare antibodies to TNF. These agents are useful in Crohn disease; additionally infliximaband, likely, adalimumabare beneficial in UC for refractory or corticosteroid-dependent disease. Several anti-interleukin antibodies and interleukins may decrease the inflammatory response and are being studied for Crohn disease. An antibody to leukocyte adhesion molecules (natalizumab) has been approved as a 2nd-line agent through a restricted prescribing program for the most refractory cases of Crohn disease; other analogs (eg, vedolizumab, tofacitinib) are also being studied.

Infliximabis given as a single IV infusion of 5 mg/kg over 2 h. It is followed by repeat infusions at wk 2 and 6. Subsequently, it is given every 8 wk. To maintain remission in many if not most patients, the dose needs to be increased or the interval needs to be shortened within a year or so. Adalimumabis given with an initial loading dose of 160 mg sc and then 80 mg sc at wk 2. After that dose, 40 mg sc is given every 2 wk. A third anti-TNF agent, certolizumab, is also approved for use in Crohn disease. Monotherapy with anti-TNF agents is clearly effective for both induction and maintenance of remission, but some studies suggest better results when anti-TNF agents are initiated in combination with a thiopurine (eg, azathioprine). Nevertheless, given the possible increase in adverse effects with combination therapy, treatment recommendations should be individualized. Corticosteroid tapering may begin after 2 wk. Adverse effects during infusion (infusion reaction) include immediate hypersensitivity reactions (eg, rash, itching, sometimes anaphylactoid reactions), fever, chills, headache, and nausea. Delayed hypersensitivity reactions have also occurred. Anti-TNF drugs given subcutaneously (eg,adalimumab) do not cause infusion reactions, although they may cause local erythema, pain, and itching (injection site reaction). Patients who are intolerant or who have lost their initial response toinfliximabmay respond to adalimumab therapy.

Several patients have died of sepsis after anti-TNF use, so these drugs are contraindicated when uncontrolled bacterial infection is present. Furthermore, TB reactivation has been attributed to these drugs; therefore, screening with PPDs and/or interferon-gamma release assay and chest x-ray is required before its use.

Lymphoma, demyelinating disease, and liver and hematologic toxicity are other potential concerns with anti-TNF antibody treatment. Other anticytokine, anti-integrin, and growth factors are under investigation, as is leukopheresis therapy to deplete activated immunocytes.

Antibiotics and probiotics:

Antibiotics may be helpful in Crohn disease but are of limited use inUC.Metronidazole500 to 750 mg po tid for 4 to 8 wk may control mild Crohn disease and help heal fistulas. However, adverse effects (particularly neurotoxicity) often preclude completion of treatment.Ciprofloxacin500 to 750 mg po bid may prove less toxic. Many experts recommendmetronidazoleand ciprofloxacin in combination.

Rifaximin, a nonabsorbable antibiotic, at a dose of 200 mg po tid or 800 mg po bid may also be beneficial as treatment for active Crohn disease.

Various nonpathogenic microorganisms (eg, commensal *Escherichia coli*, *Lactobacillus* species,*Saccharomyces*) given daily serve as probiotics and may be effective in preventing pouchitis (seeSurgery), but other therapeutic roles have yet to be clearly defined. Therapeutic infestation with the parasite *Trichuris suis* has been tried in an effort to stimulate T2-helper cell immunity and may decrease disease activity in UC.

Supportive care:

Most patients and their families are interested in diet and stress management. Although there are anecdotal reports of clinical improvement on certain diets, including one with rigid carbohydrate restrictions, controlled trials have shown no benefit. Stress management may be helpful.

6. Equipment: study room, acknowledge with protocol and procedure of colonoscopy, rectoromanoscopy and X-ray with contrast during visit to functional department (1st floor in University Clinic). Results of these investigations are provided to applicants during lesson.
7. Learning hours: 4 hours.

Plan of the lesson

I. Organizational moment (greetings, checking who is present on the lesson, announcing topic and goal of the lesson, motivating students to study the topic).

II. Control of basic knowledge (oral questioning, tests, checking of how clinical cases and workbooks are fulfilled).

2.1. Demands for applicants theoretical preparation

Applicant should know.

Didactic units list:
1. IBS, ulcerative colitis, Crohn's disease: definition.
2. Etiology, pathogenesis.
3. Clinical features of each disease.
4. Criteria of diagnostics. Roman criteria of IBS diagnostics.
5. Differential diagnosis.
6. Complications and diseases, associated with ulcerative colitis (sclerosing cholangitis, spondylitis, arthritis, dermatosis).
7. Differential treatment.
8. Primary and secondary prophylaxis.
9. Prognosis for life, convalescence and work capacity.

Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:
Tests for self-control
1. A patient 38 y.old, complains of pains in paraumbilical region, in inferolateral parts of stomach, bloating, tummy rumbling, increasing after meal, decreasing after the defecation act. Stool 1 time a day, similar to scybalous. Disturbed by tearfulness, insomnia. Was examined, no pathology during colonoscopy. Diagnosis: irritable intestine syndrome with prevalence of pains syndrome and meteorism. What symptoms of a patient is evidence of favour of this disease?
A. Insomnia, tearfulness.
B. Pains on paraumbilical region.
C. Pains in inferolateral parts of stomach, bloating, tummy rumbling. +
D. Bloating.
E. Tummyrumbling.
2. A patient 29 y.old complains of a pronounced meteorism, tenesmus, stool solid 1 time a day with much mucus. Given symptoms have been disturbing for 3 months, increase on the background of stress situations. Sclera's are subicteric. Tongue is coated with a white fur on the root. During palpation abdomen is bloated, segments of a large intestine are spasmed, painful. What objective data is evidence in favour of affection of a large intestine?
A. Subicteritiousness of sclera.
B. Tongue is coated with a white fur.
C. Segments of a large intestine are spasmed, painful.+
D. Tenesmus.
E. Stool solid 1 time a day with much mucus.
3. A 35 y.o. woman consulted a doctor about occasional pains in paraumbilical and iliac region that reduce after defecation or passage of gases. Defecation takes place up to 6 times a day, stool is not solid, with some mucus in it. Appetite is normal, she has not put off weight. First such symptoms appeared 1,5 year ago, but colonoscopy data reveals no organic changes. Objectively: abdomen is

soft, a little bit painful in the left iliac region. Blood and urine are normal. What is the preliminary diagnosis?
A. Irritable bowels syndrome +
B. Celiac disease
C. Crohn's disease
D. Pseudomembranous colitis
E. Dispancreatism
4. A 20-year-old woman has a 3-4 month history of bloody diarrhoea; stool examination proved negative for ova and parasites; stool cultures negative for clostridium, campylobacter and yersinia; normal small bowel series; edema, hyperemia and ulceration of the rectum and sigmoid colon seen on sigmoidoscopic examination. Select the most likely diagnosis:
A. Ulcerative colitis +
B. Gastroenteritis
C. Carcinoid syndrome
D. Zollinger-Ellison syndrome
E. Granulomatous colitis
5. A 54 year old male patient complains about permanent dull pain in the mesogastral region, weight loss, dark blood admixtures in the feces, constipations. He put off 10 kg within a year. In blood: erythrocytes: $3,5*10^{12}$/l, Hb- 87 g/l, leukocytes - $12,6*10^{9}$/l,stab neutrophil shift, ESR- 43 mm/h. What is the most probable diagnosis?
A. Cancer of transverse colon +
B. Gastric ulcer
C. Chronic colitis
D. Chronic pancreatitis
E. Stomach cancer
6. A 43-year-old female patient complains of unstable defecation with frequent constipations, abdominal swelling, headache, sleep disturbance. Body weight is unchanged. What disease are these clinical presentations typical for?
A. Irritable colon syndrome +
B. Chronic enteritis
C. Chronic pancreatitis
D. Chronic atrophic gastritis
E. Colorectal cancer
7. A 43 y.o. male complains of stomach pain, which relieves with defecation, and is accompanied by abdominal winds, rumbling, the feeling of incomplete evacuation or urgent need for bowel movement, constipation or diarrhea in alternation. These symptoms have lasted for over 3 months. No changes in laboratory tests. What is the most likely diagnosis?
A . Irritable bowel syndrome +
B. Spastic colitis
C. Colitis with hypertonic type dyskinesia
D. Chronic enterocolitis, exacerbation phase
E. Atonic colitis
8. A patient has clinical signs of colitis. During irrigography the disappearance of haustra, ulcerative defects in the form of barium deposits and crenation of contours, pseudopolyps were revealed. In favor of what diagnosis is it evidence?
A. Ischemic colitis.
B. Crohn's disease.
C. Nonspecific ulcerative colitis. +
D. Lymphocytic colitis.
E. Collagenic colitis.
9. A patient 54 y.old, complains of frequent, liquid stool with a mucous admixture, food debris, meteorism. The indicated symptoms increase on the background of nervousness. Notices dryness

and peeling of skin, burning sensation on a tongue tip, fragility of nails and falling out of hair. Diagnosis: malabsorption syndrome. Result of what examination confirms this syndrome?
A. Colonoscopy. +
B. Irrigoscopy.
C. Proctoscopy.
D. D-xylose test.
E. Biopsy of a mucous membrane.
10.A patient has diagnosis: nonspecific ulcerative colitis with light course. Choose medicines for the basic treatment:
A. Mesalazin, budesonide. +
B. Antibiotics, prednisolone.
C. Antibiotics, sulphonamid.
D. Cytostatics.
E. Probiotics.

III. Formation of professional skills, abilities:

3.1. content of tasks (tasks, clinical situations, etc.)

Case history #1

A 27-year-old man with a 3-month history of rectal bleeding and diarrhoea is referred for evaluation. Laboratory tests show mild anaemia, a slightly elevated sedimentation rate, and the presence of white blood cells in stool. Stool culture is negative. Colonoscopy shows continuous active inflammation with loss of vascular pattern and friability from the anal verge up to 35 cm, with a sharp cut-off. The colonic mucosa above 35 cm appears normal, as does the terminal ileum. Biopsy specimens show active chronic colitis.

Case history #2

A 16-year-old girl presents to emergency care with perianal pain and discharge. She reports a 2-year history of intermittent bloody diarrhoea with nocturnal symptoms. On examination, she is apyrexial with normal vital signs. Her abdomen is soft and slightly tender on palpation in the left lower quadrant. Rectal examination is difficult to perform due to pain, but an area of erythematous swelling is visible close to the anal margin, discharging watery pus from its apex. Several anal tags are also present.

Task: Applicant should write diagnosis, plan of investigation, carry out differential diagnosis, prescribe treatment for these case histories.

3.2. recommendations (instructions) for performing tasks (professional algorithms, orientation maps for the formation of practical skills, etc.)

Professional algorithms.

XIII. Patient's examination.

During patient's examination applicants should keep such communicative skills:
1. Friendly face expression.
2. Kind voice tone.
3. Greetings, showing concern and respect about the patient.
4. Find out patient's complaints and anamnesis .
5. Explanation of investigation results.
6. Explanation of specific actions (hospitalization, carrying out investigations) which are planned to be performed in the future.

7. Finishing of the talk.

XIV. Patient's examination and investigation algorithm.

1. It should be explained to patient which investigation will be held and indications for this investigation.
2. A doctor should receive patient's agreement on investigation.
3. A doctor should warn patient about possibilities of unpleasant feelings during investigation.
4. Results of investigation should be explained to a patient.
5. Stool studies should be obtained, including comprehensive culture and Clostridium difficile toxin assessment.
6. Of all the stool inflammatory tests available, faecal calprotectin is recommended. It is elevated when there is bowel inflammation and correlates with endoscopic and histological gradings of disease severity.
7. Full blood count, lover function tests and CRP should be checked.
8. Flexible sigmoidoscopy and colonoscopy should be performed.
9. Biopsies should be obtained at the time of endoscopy even if the mucosa appears unremarkable.
10. Serological markers: perinuclear antineutrophil cytoplasmic antibody (pANCA) and anti-Saccharomyces cerevisiae antibody (ASCA) should be checked. About 70% of patients with ulcerative colitis have positive pANCA; about 70% of patients with Crohn's disease have positive ASCA.
11. Contrast radiological studies (upper GI and small bowel series with oral contrast medium) are often used to look for CD of the small bowel.
12. Computed tomography (CT) and magnetic resonance imaging (MRI) are imaging modalities of choice.
13. If CT scans have not already been performed and small bowel radiographs are not diagnostic, CT (with intravenous and oral contrast medium) of the small bowel is indicated.
14. Technetium-99 labelled white blood cell scanning is used for diagnosis in patients unable to undergo colonoscopy. This scan highlights areas of inflammation.
15. Positron emission tomography (PET) uses fluoro-2-deoxy-D-glucose (FDG) to identify areas of abnormal metabolism. It may have a role as a non-invasive test in early evaluation of Crohn's disease in patients unable to tolerate endoscopic assessment.
16. Oesophagogastroduodenoscopy (OGD) should be performed to evaluate patients with predominantly upper GI symptoms.
17. Capsule enteroscopy should be considered when imaging, colonoscopy, and OGD fail to establish diagnosis.

XV. Step-by-step algorithm of treatment.

1. A patient should informed be about necessity of the prescribed treatment.
2. Dosages, drugs intake regimens, duration of treatment, side effects of the prescribed therapy should be kindly explained to patient.
3. Treatment of mild-to-moderate distal disease is with topical mesalazine or topical corticosteroids and oral mesalazine (5-aminosalicylic acid [5-ASA]). Rectal 5-ASA should be considered as the first-line therapy for patients with mild-to-moderately active distal ulcerative colitis.
4. Topical therapy with oral mesalazine therapy is more effective than either alone.
5. Second-generation corticosteroids, such as budesonide multi-matrix system, are starting to emerge as a primary treatment option in mild-to-moderate ulcerative colitis.
6. Remission can be maintained with topical mesalazine suppositories in combination with oral mesalazine.
7. Oral beclometasone may also be considered for maintenance of remission depending on patient preference.
8. In severe ulcerative colitis patients should be treated with topical therapy and oral 5-ASA at maximal doses, and systemic corticosteroids. If symptoms persist despite maximal doses of oral and topical therapy, the patient should be admitted and treated with parenteral corticosteroids.

9. Patients with fulminant colitis have >10 bowel movements daily with continuous or massive uncontrolled bleeding, or severe toxicity including the development of toxic megacolon should be prescribed parenteral corticosteroids.
10. Patients who are relatively stable and respond partially or sub-optimally to intravenous corticosteroids within 72 hours should be considered for infliximab or ciclosporin induction therapy.
11. Antidiarrhoeal agents should be avoided in patients with active colitis, given the risk of developing toxic megacolon.
12. Immunomodulators (azathioprine, mercaptopurine, methotrexate) are commonly used in combination with corticosteroids to help induce remission in active Crohn's disease.
13. The anti-TNF monoclonal antibodies infliximab and adalimumab have shown good results in the treatment of Crohn's disease.
14. Methotrexate, given intramuscularly, can be used for maintenance of remission in Crohn's disease and appears to be safe.

3.3. requirements for applicant work results.

As a results of studying students must perform the following:
-possess skills of communication and clinical examination of a patient with IBS, ulcerative colitis and Crohn's disease;
-collect data on patient complaints, medical history, life history;
-evaluate information about the diagnosis of IBS, ulcerative colitis and Crohn's disease using a standard procedure, based on the results of laboratory, instrumental and morphological studies;
-determine the list of required clinical, laboratory, instrumental and morphological studies and evaluate their results;
- identify the leading clinical symptom or syndrome;
- establish the most probable or syndrom diagnosis;
-assign laboratory and instrumental investigations for patient;
-carry out differential diagnosis in IBS, ulcerative colitis and Crohn's disease;
-establish preliminary and clinical diagnosis;
- determine the principles of treatment, diet regimen for the patient.

3.4. control materials for the final stage of the lesson.

Work 1
1. Collection of complaints, anamnesis, examination of a patient with chronic colon diseases and nonspecific colitis.
2. Detection of clinical and instrumental symptoms.
3. Grouping symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data.
6. Carrying out a differential diagnosis.
7. Formulation of the clinical diagnosis.
8. Write a prescription list for patients diagnosed with nonspecific colitis and Crohn's disease, which would include diet and prescribed drugs.
9. Determining of the disability degree.

Work 2.
Assignment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the department library with thematic literature.
The student fills in the protocol of the patient's examination. An example of the initial examination of the patient is attached.

The tests for self-control with standard answers.
1. A 35 y.o. woman consulted a doctor about occasional pains in paraumbilical and iliac region that reduce after defecation or passage of gases. Defecation takes place up to 6 times a day, stool is not solid, with some mucus in it. Appetite is normal, she has not put off weight. First such symptoms appeared 1,5 year ago, but colonoscopy data reveals no organic changes. Objectively: abdomen is soft, a little bit painful in the left iliac region. Blood and urine are normal. What is the preliminary diagnosis?
A Irritable bowels syndrome
B Celiac disease
C Crohn's disease
D Pseudomembranous colitis
E Dispancreatism
2. A 45-year-old female patient complains of frequent liquid stools with a lot of mucus, pus and blood; pain across the abdomen, loss of 7 kg within 6 months. She has a 1-year history of non-specific ulcerative colitis. What group of drugs should be preferred for this patient?
A Antibacterial
B Corticosteroids
C Sulfonamides
D Nitrofurans
E Polyenzymes
3. A 51-year-old female patient complains of frequent defecation and liquid blood-streaked stools with mucus admixtures, diffuse pain in the inferolateral abdomen, 6 kg weight loss over the previous month. Objectively: body temperature - 37,4ºC, malnutrition, skin is pale and dry. Abdomen is soft, sigmoid is painful and spasmodic, makes a rumbling sound. Liver is dense, painful, extends 3 cm below the costal margin. What is the most likely diagnosis?
A Sprue
B Bacillary dysentery
C Non-specific ulcerative colitis
D Intestinal enzymopathy
E Helminthic invasion
4. A 43-year-old female patient complains of unstable defecation with frequent constipations, abdominal swelling, headache, sleep disturbance. Body weight is unchanged. What disease are these clinical presentations typical for?
A Chronic atrophic gastritis
B Chronic enteritis
C Chronic pancreatitis
D Irritable bowel syndrome
E Colorectal cancer
5. A 43 y.o. male complains of stomach pain, which relieves with defecation, and is accompanied by abdominal winds, rumbling, the feeling of incomplete evacuation or urgent need for bowel movement, constipation or diarrhea in alternation. These symptoms have lasted for over 3 months. No changes in laboratory tests. What is the most likely diagnosis?
A Atonic colitis
B Spastic colitis
C Colitis with hypertonic type dyskinesia
D Chronic enterocolitis, exacerbation phase
*E*Irritable bowel syndrome

6. A 28 y.o. man fell seriously ill, he feels chill, has got a fever, body temperature raised up to $38,5^0$C, paroxysmal pain in the left iliac region, frequent defecation in form of fluid bloody and mucous mass. Abdomen palpation reveals painfulness in its left half, sigmoid colon is spasmed. What is the most probable diagnosis?
A Acute dysentery
B Amebiasis
C Colibacillosis
D Nonspecific ulcerative colitis
E Malignant tumors of large intestine
7. A 20-year-old woman has a 3-4 month history of bloody diarrhoea; stool examination proved negative for ova and parasites; stool cultures negative for clostridium, campylobacter and yersinia; normal small bowel series; edema, hyperemia and ulceration of the rectum and sigmoid colon seen on sigmoidoscopic examination. Select the most likely diagnosis:
A Gastroenteritis
B Ulcerative colitis
C Carcinoid syndrome
D Zollinger-Ellison syndrome
E Granulomatous colitis
8. A 41 year old woman has suffered from nonspecific ulcerative colitis for 5 years. On rectoromanoscopy: evident inflammatory process of lower intestinal parts, pseudopolyposive changes of mucous membrane. In blood: WBC- $9,8*10^9$/l, RBC- $3,0*10^{12}$/l, ESR - 52 mm/hour. What medication provides pathogenetic treatment of this patient?
A Vikasolum
B Motilium
C Sulfosalasine
D Linex
E Kreon

Standard answers: 1-A, 2-B, 3-C, 4-D, 5-E, 6-A, 7-B, 8-C.

IV. Summarizing, announcing the final grade, announcing the task for the next lesson.
Recommended resources:
- Basic literature source:
1. NICE guideline. Crohn's disease: management 2019 https://www.nice.org.uk/guidance/ng129
2. NICE guideline. Ulcerative colitis: management 2019
https://www.nice.org.uk/guidance/ng130
3. Rubin DT, Ananthakrishnan AN, Siegel CA, et al. ACG clinical guideline: ulcerative colitis in adults. Am J Gastroenterol. 2019 Mar;114(3):384-413

- Additional literature source:
1. Cholapranee A, Hazlewood GS, Kaplan GG, et al. Systematic review with meta-analysis: comparative efficacy of biologics for induction and maintenance of mucosal healing in Crohn's disease and ulcerative colitis controlled trials. Aliment Pharmacol Ther. 2017 May;45(10):1291-302

Appendix 1

Example of the primary examination of the patient

Passport data: name and surname, age

Complaints:

On general weakness, fever up to subfebrile rates, cramping abdominal pain, mainly in the left half, weight loss, liquid stool with blood admixture up to 5 times a day.

Anamnesis morbi

The patient is sick for 3 years, previously did not look for medical help, was not examined. The last exacerbation was about 1.5 months, when impurities of blood and mucus appeared in the feces.

Anamnesis vitae

Living conditions are satisfactory. Botkin's disease, tuberculosis, sexually transmitted diseases, malaria denies.

Professional anamnesis: not burdened.

Hereditary history is not burdened.

Pave not been in contact with infectious patients for the last 3 days. He has not left the country in the last 3 years.

***Hereditary history**: not burdened*

Neurological history

At the time of examination signs of focal neurological symptoms were not detected.

***Allergic history**: not burdened*

Epidemiology

Tuberculosis, malaria, viral hepatitis, Botkin's disease, veneral disease, HIV, AIDS, pediculosis – denies.

***Oncoanamnesis**: denies.*

***Insurance anamnesis**: There is no need to issue a seak leave, for the last 12 months a seak leave document has not been issued in this regard.*

***Postponed operations**: denies.*

***Bad habits**: smokes for 10 years, 1 pack a day*

Examination of organ systems:

GENERAL Condition: satisfactory

CONSCIOUSNESS: clear

Body shape: normostenic

Fatness: low nutrition

POSITION OF THE PATIENT: active

BODY TEMPERATURE: 36.6 C. Signs of alcohol intoxication - no

SKIN: Skin of pale color, clean. Tissue turgor is normal. Skin pigmentation: depigmentation - no. Rash: no; other changes in the skin: no.

Visible mucous membranes: Normal color

LYMPH NODES: not enlarged

THYROID GLAND: no pathology

Oncological examination was performed, no visual forms of oncopathology were detected

Cardiovascular system:

PERCUSSION OF THE HEART: the limits of relative cardiac dullness: right on the right edge of the sternum, upper -III rib on the left parasternalis line, left - 1 cm outward from the left mediaclavicularis line in the V intercostal space

HEART activity: rhythmic, heart rate - 74 per 1 min. Pulse 74 in 1 min. Heart tones: muffled

HEART MURMURS: no

EDEMA: no

BP 125 / 85 mm Hg

EXAMINATION OF ARTERIES: no pathology

VEIN STUDY: no pathology

RESPIRATORY SYSTEM:

BREATHING: no dyspnea at rest, RR 16 in 1 min.
Sputum: no
CHEST: cylindrical, not deformed. Intercostal spaces: NOT smoothed. Participation of additional muscles: no, RR – 16 in 1 min. SpO2 = 98%
Percussion over the lungs: clear lung sound.
PULMONARY AUSCULTATION: vesicular breathing over both lungs. Pleural friction noise - no
DIGESTIVE SYSTEM:
TONGUE: wet; covered with grey plaque. There are superficial painful ulcers on the mucosa of cheeks.
Tonsils: not enlarged
STOMACH: participates in the act of breathing. No hernia. Pulsation in the epigastrium - no. There is no dilation of the subcutaneous veins
Palpation: moderately painful in left iliac region.
Pathological symptoms: not detected
Liver: not enlarged
Gallbladder: not palpable
Pancreas: painless
Spleen: not palpable,
PERCUTIONAL SOUND OVER THE ABDOMINAL CAVITY: unchanged,
FECES: normal, no pathological impurities
URINARY SYSTEM:
Palpation of the kidneys: not palpable
Pasternatsky's symptom is negative on both sides.
Urination: free, painless, frequency per day: 3-4 times.
Urinary incontinence: no.
SENSES:
SIGHT: not violated (OU). There is no other pathology
HEARING: normal, no deafness, pain: no. Tinnitus: no.
Musculoskeletal system:
Pathology of the musculoskeletal system was not detected
On the basis of complaints, anamnesis, objective examination, it is possible to make a preliminary diagnosis:
Krohn's disease
Plan of investigation
general blood test, general urine test, glycemia level (8.00, 13.00, 17.00, 21.00)
Biochemistry: liver tests, glucose, transaminases, protein, lipid spectrum, coagulogram, amylase, AF, LDH, GGT, CPK, serum iron, potassium, CRP, vitamins A, D, E, K, B12, folic acid, ultrasound of pelvis, CT of abdomen, colonoscopy with biopsy, rectoromanoscopy, videocapsule endography.
Consultation of a neurologist, gastroenterologist.
Treatment plan
Drug therapy:
- Loperamide 2 mg / day 8-10 days
- Mesalazine in suppositories 0.5 x3 times a day for 6-8 weeks
- Budenofalk - 2 mg rectally once a day for 6-8 weeks

Appendix 2

Tests of basic knowledge level in KROK format

Theme 22. Chronic colon diseases. IBS and nonspecific colitis

1. A 43-year-old female patient complains of unstable defecation with frequent constipations, abdominal swelling, headache, sleep disturbance. Body weight is unchanged. What disease are these clinical presentations typical for?

A Chronic atrophic gastritis
B Chronic enteritis
C Chronic pancreatitis
D Irritable bowel syndrome
E Colorectal cancer

2. A 43 y.o. male complains of stomach pain, which relieves with defecation, and is accompanied by abdominal winds, rumbling, the feeling of incomplete evacuation or urgent need for bowel movement, constipation or diarrhea in alternation. These symptoms have lasted for over 3 months. No changes in laboratory tests. What is the most likely diagnosis?

A Atonic colitis
B Spastic colitis
C Colitis with hypertonic type dyskinesia
D Chronic enterocolitis, exacerbation phase
E Irritable bowel syndrome

3. A 28 y.o. man fell seriously ill, he feels chill, has got a fever, body temperature raised up to $38,5^0$C, paroxysmal pain in the left iliac region, frequent defecation in form of fluid bloody and mucous mass. Abdomen palpation reveals painfulness in its left half, sigmoid colon is spasmed. What is the most probable diagnosis?

A Acute dysentery
B Amebiasis
C Colibacillosis
D Nonspecific ulcerative colitis
E Malignant tumors of large intestine

4. A 20-year-old woman has a 3-4 month history of bloody diarrhoea; stool examination proved negative for ova and parasites; stool cultures negative for clostridium, campylobacter and yersinia; normal small bowel series; edema, hyperemia and ulceration of the rectum and sigmoid colon seen on sigmoidoscopic examination. Select the most likely diagnosis:

A Gastroenteritis
B Ulcerative colitis
C Carcinoid syndrome
D Zollinger-Ellison syndrome
E Granulomatous colitis

5. A 41 year old woman has suffered from nonspecific ulcerative colitis for 5 years. On rectoromanoscopy: evident inflammatory process of lower intestinal parts, pseudopolyposive changes of mucous membrane. In blood: WBC- $9,8*10^9$/l, RBC- $3,0*10^{12}$/l, ESR - 52 mm/hour. What medication provides pathogenetic treatment of this patient?

A Vikasolum
B Motilium
C Sulfosalasine
D Linex
E Kreon

6. A 35 y.o. woman consulted a doctor about occasional pains in paraumbilical and iliac region that reduce after defecation or passage of gases. Defecation takes place up to 6 times a day, stool is not solid, with some mucus in it. Appetite is normal, she has not put off weight. First such symptoms appeared 1,5 year ago, but colonoscopy data reveals no organic changes. Objectively: abdomen is

soft, a little bit painful in the left iliac region. Blood and urine are normal. What is the preliminary diagnosis?
A Irritable bowels syndrome
B Celiac disease
C Crohn's disease
D Pseudomembranous colitis
E Dispancreatism
7. A 45-year-old female patient complains of frequent liquid stools with a lot of mucus, pus and blood; pain across the abdomen, loss of 7 kg within 6 months. She has a 1-year history of non-specific ulcerative colitis. What group of drugs should be preferred for this patient?
A Antibacterial
B Corticosteroids
C Sulfonamides
D Nitrofurans
E Polyenzymes
8. A 51-year-old female patient complains of frequent defecation and liquid blood-streaked stools with mucus admixtures, diffuse pain in the inferolateral abdomen, 6 kg weight loss over the previous month. Objectively: body temperature - 37,4ºC, malnutrition, skin is pale and dry. Abdomen is soft, sigmoid is painful and spasmodic, makes a rumbling sound. Liver is dense, painful, extends 3 cm below the costal margin. What is the most likely diagnosis?
A Sprue
B Bacillary dysentery
C Non-specific ulcerative colitis
D Intestinal enzymopathy
E Helminthic invasion
9. A patient has clinical signs of colitis. During irrigography the disappearance of haustra, ulcerative defects in the form of barium deposits and crenation of contours, pseudopolyps were revealed. In favor of what diagnosis is it evidence?
A Ischemic colitis.
B Crohn's disease.
C Nonspecific ulcerative colitis.
D Lymphocytic colitis.
E Collagenic colitis.
10. A patient 54 y.old, complains of frequent, liquid stool with a mucous admixture, food debris, meteorism. The indicated symptoms increase on the background of nervousness. Notices dryness and peeling of skin, burning sensation on a tongue tip, fragility of nails and falling out of hair. Diagnosis: malabsorption syndrome. Result of what examination confirms this syndrome?
A Colonoscopy.
B Irrigoscopy.
C Proctoscopy.
D D-xylose test.
E Biopsy of a mucous membrane.

Practical lesson #23
1. Theme: Gallstone disease, chronic cholecystitis and functional biliar diskinesies

2. Goal:
To study:
- Etiology, pathogenesis of gallstone disease, chronic cholecystitis, classification, clinic, complications, diagnosis and treatment.
- Functional biliary dyskinesies: classification, clinic, complications, diagnosis and treatment;
- General, dietary and pharmacological recommendations.
- Classification and pharmacological peculiarity of drug, which are used in biliary diseases.

Basic concepts. Gallstone disease and chronic cholecystitis: definition, aetiology, pathogenesis. Diagnostics and differential diagnostics. Treatment. Complications. Prognosis. Functional biliary dyskinesies: classification, clinic, complications, diagnosis and treatment.

Cholelithiasis is the presence of one or more calculi (gallstones) in the gallbladder. In developed countries, about 10% of adults and 20% of people > 65 yr have gallstones. Gallstones tend to be asymptomatic. The most common symptom is biliary colic; gallstones do not cause dyspepsia or fatty food intolerance. More serious complications include cholecystitis; biliary tract obstruction (by stones in the bile ducts), sometimes with infection (cholangitis); and gallstone pancreatitis. Diagnosis is usually by ultrasonography. If cholelithiasis causes symptoms or complications, cholecystectomy is necessary.
Risk factors for gallstones include female sex, obesity, increased age, American Indian ethnicity, a Western diet, rapid weight loss, and a family history. Most disorders of the biliary tract result from gallstones.
Pathophysiology
Biliary sludge is often a precursor of gallstones. It consists of Ca bilirubinate (a polymer of bilirubin), cholesterol microcrystals, and mucin. Sludge develops during gallbladder stasis, as occurs during pregnancy or use of TPN. Most sludge is asymptomatic and disappears when the primary condition resolves. Alternatively, sludge can evolve into gallstones or migrate into the biliary tract, obstructing the ducts and leading to biliary colic, cholangitis, or pancreatitis.
There are several types of gallstones.
Cholesterol stones account for > 85% of gallstones in the Western world. For cholesterol gallstones to form, the following is required:
- Bile must be supersaturated with cholesterol. Normally, water-insoluble cholesterol is made water soluble by combining with bile salts and lecithin to form mixed micelles. Supersaturation of bile with cholesterol most commonly results from excessive cholesterol secretion (as occurs in obesity or diabetes) but may result from a decrease in bile salt secretion (eg, in cystic fibrosis because of bile salt malabsorption) or in lecithin secretion (eg, in a rare genetic disorder that causes a form of progressive intrahepatic familial cholestasis).
- The excess cholesterol must precipitate from solution as solid microcrystals. Such precipitation in the gallbladder is accelerated by mucin, a glycoprotein, or other proteins in bile.
- The microcrystals must aggregate and grow. This process is facilitated by the binding effect of mucin forming a scaffold and by retention of microcrystals in the gallbladder with impaired contractility due to excess cholesterol in bile.
Black pigment stones are small, hard gallstones composed of Ca bilirubinate and inorganic Ca salts (eg, Ca carbonate, Ca phosphate). Factors that accelerate stone development include alcoholic liver disease, chronic hemolysis, and older age.

Brown pigment stones are soft and greasy, consisting of bilirubinate and fatty acids (Ca palmitate or stearate). They form during infection, inflammation, and parasitic infestation (eg, liver flukes in Asia).

Gallstones grow at about 1 to 2 mm/yr, taking 5 to 20 yr before becoming large enough to cause problems. Most gallstones form within the gallbladder, but brown pigment stones form in the ducts. Gallstones may migrate to the bile duct after cholecystectomy or, particularly in the case of brown pigment stones, develop behind strictures as a result of stasis and infection.

Symptoms and Signs

About 80% of people with gallstones are asymptomatic. The remainder have symptoms ranging from a characteristic type of pain (biliary colic) to cholecystitis to life-threatening cholangitis. Biliary colic is the most common symptom.

Stones occasionally traverse the cystic duct without causing symptoms. However, most gallstone migration leads to cystic duct obstruction, which, even if transient, causes biliary colic. Biliary colic characteristically begins in the right upper quadrant but may occur elsewhere in the abdomen. It is often poorly localized, particularly in diabetics and the elderly. The pain may radiate into the back or down the arm. Episodes begin suddenly, become intense within 15 min to 1 h, remain at a steady intensity (not colicky) for up to 12 h (usually < 6 h), and then gradually disappear over 30 to 90 min, leaving a dull ache. The pain is usually severe enough to send patients to the emergency department for relief. Nausea and some vomiting are common, but fever and chills do not occur unless cholecystitis has developed. Mild right upper quadrant or epigastric tenderness may be present; peritoneal findings are absent. Between episodes, patients feel well.

Although biliary colic can follow a heavy meal, fatty food is not a specific precipitating factor. Nonspecific GI symptoms, such as gas, bloating, and nausea, have been inaccurately ascribed to gallbladder disease. These symptoms are common, having about equal prevalence in cholelithiasis, peptic ulcer disease, and functional GI disorders.

Little correlation exists between the severity and frequency of biliary colic and pathologic changes in the gallbladder. Biliary colic can occur in the absence of cholecystitis. If colic lasts > 12 h, particularly if it is accompanied by vomiting or fever, acute cholecystitis or pancreatitis is likely.

Diagnosis

- Ultrasonography

Gallstones are suspected in patients with biliary colic. Abdominal ultrasonography is the method of choice for detecting gallbladder stones; sensitivity and specificity are 95%. Ultrasonography also accurately detects sludge. CT, MRI (see MRI), and oral cholecystography (rarely available now, although quite accurate) are alternatives. Endoscopic ultrasonography accurately detects small gallstones (< 3 mm) and may be needed if other tests are equivocal.

Laboratory tests usually are not helpful; typically, results are normal unless complications develop.

Asymptomatic gallstones and biliary sludge are often detected incidentally when imaging, usually ultrasonography, is done for other reasons. About 10 to 15% of gallstones are calcified and visible on plain x-rays.

Prognosis

Patients with asymptomatic gallstones become symptomatic at a rate of about 2%/yr. The symptom that develops most commonly is biliary colic rather than a major biliary complication. Once biliary symptoms begin, they are likely to recur; pain returns in 20 to 40% of patients/yr, and about 1 to 2% of patients/yr develop complications such as cholecystitis, choledocholithiasis, cholangitis, and gallstone pancreatitis.

Treatment

- ✓ For symptomatic stones: Laparoscopic cholecystectomy or sometimes stone dissolution using ursodeoxycholic acid
- ✓ For asymptomatic stones: Expectant management

Most asymptomatic patients decide that the discomfort, expense, and risk of elective surgery are not worth removing an organ that may never cause clinical illness. However, if symptoms occur,

gallbladder removal (cholecystectomy) is indicated because pain is likely to recur and serious complications can develop.

Surgery:

Surgery can be done with an open or a laparoscopic technique.

Open cholecystectomy, which involves a large abdominal incision and direct exploration, is safe and effective. Its overall mortality rate is about 0.1% when done electively during a period free of complications.

Laparoscopic cholecystectomy is the treatment of choice. Using video endoscopy and instrumentation through small abdominal incisions, the procedure is less invasive than open cholecystectomy. The result is a much shorter convalescence, decreased postoperative discomfort, improved cosmetic results, yet no increase in morbidity or mortality. Laparoscopic cholecystectomy is converted to an open procedure in 2 to 5% of patients, usually because biliary anatomy cannot be identified or a complication cannot be managed. Older age typically increases the risks of any type of surgery.

Cholecystectomy effectively prevents future biliary colic but is less effective for preventing atypical symptoms such as dyspepsia. Cholecystectomy does not result in nutritional problems or a need for dietary limitations. Some patients develop diarrhea, often because bile salt malabsorption in the ileum is unmasked. Prophylactic cholecystectomy is warranted in asymptomatic patients with cholelithiasis only if they have large gallstones (> 3 cm) or a calcified gallbladder (porcelain gallbladder); these conditions increase the risk of gallbladder carcinoma.

Stone dissolution:

For patients who decline surgery or who are at high surgical risk (eg, because of concomitant medical disorders or advanced age), gallbladder stones can sometimes be dissolved by ingesting bile acids orally for many months. The best candidates for this treatment are those with small, radiolucent stones (more likely to be composed of cholesterol) in a functioning nonobstructed gallbladder (indicated by normal filling detected during cholescintigraphy or oral cholecystography or by absence of stones in the neck).

Ursodeoxycholic acid 4 to 5 mg/kg po bid or 3 mg/kg po tid (8 to 10 mg/kg/day) dissolves 80% of tiny stones < 0.5 cm in diameter within 6 mo. For larger stones (the majority), the success rate is much lower, even with higher doses of ursodeoxycholic acid. Further, after successful dissolution, stones recur in 50% within 5 yr. Most patients are thus not candidates and prefer laparoscopic cholecystectomy. However, ursodeoxycholic acid 300 mg po bid can help prevent stone formation in morbidly obese patients who are losing weight rapidly after bariatric surgery or while on a very low calorie diet.

Stone fragmentation (extracorporeal shock wave lithotripsy) to assist stone dissolution and clearance is now unavailable.

Key Points

- ✓ In developed countries, about 10% of adults and 20% of people > 65 yr have gallstones, but 80% are asymptomatic.
- ✓ Abdominal ultrasonography is 95% sensitive and specific for detecting gallbladder stones.
- ✓ Once symptoms develop (usually biliary colic), pain returns in 20 to 40% of patients/yr.
- ✓ Treat most patients who have symptomatic gallstones with laparoscopic cholecystectomy.

Postcholecystectomy syndrome is occurrence of abdominal symptoms after cholecystectomy.

Postcholecystectomy syndrome occurs in 5 to 40% of patients. It refers to presumed gallbladder symptoms that continue or that develop after cholecystectomy or to other symptoms that result from cholecystectomy. Removal of the gallbladder, the storage organ for bile, normally has few adverse effects on biliary tract function or pressures. In about 10%, biliary colic appears to result from functional or structural abnormalities of the sphincter of Oddi, resulting in altered biliary pressures or heightened sensitivity.

The most common symptoms are dyspepsia or otherwise nonspecific symptoms rather than true biliary colic. Papillary stenosis, which is rare, is fibrotic narrowing around the sphincter, perhaps caused by trauma and inflammation due to pancreatitis, instrumentation (eg, ERCP), or prior

passage of a stone. Other causes include a retained bile duct stone, pancreatitis, and gastroesophageal reflux.

Diagnosis

- ✓ ERCP with biliary manometry or biliary nuclear scanning
- ✓ Exclusion of extrabiliary pain

Patients with postcholecystectomy pain should be evaluated as indicated for extrabiliary as well as biliary causes. If the pain suggests biliary colic, alkaline phosphatase, bilirubin, ALT, amylase, and lipase should be measured, and ERCP with biliary manometry or biliary nuclear scanning should be done. Elevated liver enzymes suggest sphincter of Oddi dysfunction; elevated amylase and lipase suggest dysfunction of the sphincter's pancreatic portion.

Dysfunction is best detected by biliary manometry done during ERCP, although ERCP has a 15 to 30% risk of inducing pancreatitis. Manometry shows increased pressure in the biliary tract when pain is reproduced. A slowed hepatic hilum-duodenal transit time on a scan also suggests sphincter of Oddi dysfunction. Diagnosis of papillary stenosis is based on a clear-cut history of recurrent episodes of biliary pain and abnormal liver (or pancreatic) enzyme tests.

Treatment

- Sometimes endoscopic sphincterotomy

Endoscopic sphincterotomy can relieve recurrent pain due to sphincter of Oddi dysfunction, especially if due to papillary stenosis. It is controversial for patients who have postcholecystectomy pain and no objective abnormalities.

Chronic cholecystitis is long-standing gallbladder inflammation almost always due to gallstones.

Chronic cholecystitis almost always results from gallstones and prior episodes of acute cholecystitis (even if mild). Damage ranges from a modest infiltrate of chronic inflammatory cells to a fibrotic, shrunken gallbladder. Extensive calcification due to fibrosis is called porcelain gallbladder.

Symptoms and Signs

Gallstones intermittently obstruct the cystic duct and so cause recurrent biliary colic. Such episodes of pain are not necessarily accompanied by overt gallbladder inflammation; the extent of inflammation does not correlate with the intensity or frequency of biliary colic. Upper abdominal tenderness may be present, but usually fever is not. Fever suggests acute cholecystitis. Once episodes begin, they are likely to recur.

Diagnosis

- Ultrasonography

Chronic cholecystitis is suspected in patients with recurrent biliary colic plus gallstones. Ultrasonography or another imaging test usually shows gallstones and sometimes a shrunken, fibrotic gallbladder. The diagnosis is made in patients with a history of recurrent biliary colic and ultrasonographic evidence of gallstones. Cholescintigraphy may show nonvisualization of the gallbladder but is less accurate.

Treatment

- Laparoscopic cholecystectomy

Laparoscopic cholecystectomy is indicated to prevent symptom recurrence and further biliary complications. This procedure is particularly appropriate for the porcelain gallbladder associated with gallbladder carcinoma.

Acalculous biliary pain is biliary colic without gallstones, resulting from structural or functional disorders; it is sometimes treated with laparoscopic cholecystectomy.

Biliary colic can occur in the absence of gallstones, particularly in young women. Acalculous biliary pain accounts for up to 15% of laparoscopic cholecystectomies. Common causes of such biliary pain include the following:

- ✓ Microscopic stones—not detected by routine abdominal ultrasonography
- ✓ Abnormal gallbladder emptying
- ✓ An overly sensitive biliary tract
- ✓ Sphincter of Oddi dysfunction

- ✓ Hypersensitivity of the adjacent duodenum
- ✓ Possibly gallstones that have spontaneously passed

Some patients eventually develop other functional GI disorders.

Diagnosis

- ✓ Unclear
- ✓ Usually ultrasonography and sometimes cholescintigraphy and/or ERCP

The best diagnostic approach remains unclear.

Acalculous biliary pain is suspected in patients with biliary colic when diagnostic imaging cannot detect gallstones. Imaging should include ultrasonography and, where available, endoscopic ultrasonography (for small stones < 1 cm).

Abnormal laboratory tests may reveal evidence of a biliary tract abnormality (eg, elevated alkaline phosphatase, bilirubin, ALT, or AST) or a pancreatic abnormality (eg, elevated lipase) during an episode of acute pain. Cholescintigraphy with cholecystokinin infusion measures gallbladder emptying (ejection fraction); potentially interfering drugs such as Ca channel blockers, opioids, and anticholinergics should not be used. ERCP with biliary manometry detects sphincter of Oddi dysfunction.

Treatment

- Unclear but sometimes laparoscopic cholecystectomy

Laparoscopic cholecystectomy improves outcomes for patients with microscopic stones and possibly abnormal gallbladder motility. The role of laparoscopic cholecystectomy or endoscopic sphincterotomy remains problematic. Drug therapies have no proven benefit.

Equipment: study room, ultrasound system "Mylab Six CristaLine". Students acknowledge with protocol and procedure of gallbladder and biliary tract investigation, visit functional department (1st floor in University Clinic). Results of these investigations are provided to students during lesson.

Learning hours: 4 hours.

Plan of the lesson

I. Organizational moment (greetings, checking who is present on the lesson, announcing topic and goal of the lesson, motivating applicants to study the topic).

II. Control of basic knowledge (oral questioning, tests, checking of how clinical cases and workbooks are fulfilled).

2.1. Demands for applicants theoretical preparation

Applicant should know.

Didactic units list:

1. Gallstone disease, chronic cholecystitis and functional biliary dyskinesies: definition.
2. Etiology, pathogenesis.
3. Clinical features of each disease.
4. Criteria of diagnostics.
5. Differential diagnosis.
6. Complications of gallstone disease and chronic cholecystitis.
7. Treatment approaches and strategies.
8. Primary and secondary prophylaxis.
9. Prognosis for life, convalescence and work capacity.

Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Tests for self-control

1. A 50 year old woman complained of attacks of right subcostal pain after fatty meal she has been suffering from for a year. Last week the attacks repeated every day and became more painful. What diagnostic study would you recommend?

A. Ultrasound examination of the gallbladder +

B. Liver function tests
C. X-ray examination of the gastrointestinal tract
D. Ultrasound study of the pancreas
E. Blood cell count
2. A 60-year-old woman, mother of 6 children, developed a sudden onset of upper abdominal pain radiating to the back, accompanied by nausea, vomiting, fever and chills. Subsequently, she noticed yellow discoloration of her sclera and skin. On physical examination the patient was found to be febrile with T 38,9ºC, along with right upper quadrant tenderness. The most likely diagnosis is:
A. Choledocholithiasis +
B. Benign biliary stricture
C. Malignant biliary stricture
D. Carcinoma of the head of the pancreas
E. Choledochal cyst
3. The complications of acute cholecystitis which require surgical intervention are as follows EXCEPT:
A. Jaundice +
B. Empyema of the gall-bladder
C. Emphysematous gall-bladder
D. Gall-bladder perforation
E. Cholangitis conditioned by the presence of stones in the bile tract
4. A 37-year-old patient has sudden acute pain in the right epigastric area after having fatty food. What method of radiological investigation is to be used on the first stage of examining the patient?
A. Ultrasonic +
B. Roentgenological
C. Radionuclid
D. Magnetic-resonance
E. Thermographic
5.A 50-year-old patient complains about having pain attacks in the right subcostal area for about a year. He pain arises mainly after taking fattening food. Over the last week the attacks occurred daily and became more painful. On the 3rd day of hospitalization the patient presented with icteritiousness of skin and scleras, light-colored feces and dark urine. In blood: neutrophilic leukocytosis -13,1*10^9, ESR- 28 mm/h. What is the most likely diagnosis?
A. Chronic calculous cholecystitis +
B. Chronic recurrent pancreatitis
C. Fatty degeneration of liver
D. Chronic cholangitis, exacerbation stage
E. Hypertensive dyskinesia of gallbladder
6. A patient 48 y.o., complains of dull pain in a right hypochondrium after meal, especially fatty, fried, smoked. Considers himself a sick person for 12 years. During objective exmination abdomen is slightly bloated, painful in a right hypochondrium. Liver at the edge of a costal margin, painfless. Spleen isn't palpable. Positive symptoms of Kehr, Murphy, Ortner are found. What disease should one think of?
A. Ulcerative disease of a duodenum, active phase.
B. Chronic pancreatitis in phase of exacerbation.
C. Chronic gastritis in phase of exacerbation.
D. Chronic cholecystitis in phase of remission.
E. Chronic cholecystitis in phase of exacerbation.+
7. A patient 38 y.old, had US of a gallbladder whose walls are thickened, echogenicity is increasd, double-contour of a gallbladder in a lumen – biliary sludge. What are these changes evidence of?
A. Hypermotor dyskinesia of a gallbladder.
B. Hypomotor dyskinesia of a gallbladder.
C. Chronic inflammation of a gallbladder.+

D. Tumour of a gallbladder.
E. Empyema of a gallbladder.
8. A patient had the following results during US of organs of abdominal cavity: gallbladder isn't enlarged. Echo suspension is detected. A chronic cholecystitis is supected. What disease should the differential diagnostics is done with?
A. Gallbladder empyema.
B. Tumour of a gallbladder.+
C. Cholelithiasis.
D. Hydrops of gallbladder.
E. Cholesterosis of a gallbladder.
9. A patient 37 y.old, has diagnosis: chronic noncalculous cholecystitis with geneticaly-hypertonic dyskinesia of a gallbladder. What group of medicines should be indicated for this patient?
A. Blockers of H2-histamine receptors.
B. Proton pumps inhibitors.
C. Enzymatic drugs.
D. Myotropic spasmolytics.
E. Cholekinetics.+
10. A patient has a chronic noncalculous cholecystitis in the phase of exacerbation. Complains with intensive pain in a right hypochondrium, nausea, vomiting, rise of temperature to 38,5^{0}C. Blood: leukocytes — 18 G/l,stab— 15%, ESR — 30 мм/h; total bilirubin — 22 мсmol/l, direct bilirubim — 4,2 мсmol/l. Development of what disease of a patient can be suspected?
A. Gangrene of a gallbladder.
B. Obstructive jaundice.
B. Chronic hepatitis.
D. Gallbladder empyema.+
E. Chronic pancreatitis.
III. Formation of professional skills, abilities:
3.1. content of tasks (tasks, clinical situations, etc.)
Case history #1
A 20-year-old obese woman with a 2-year history of gallstones presents to the emergency department with severe, constant right upper quadrant (RUQ) pain, nausea, and vomiting after eating fried chicken for dinner. She denies any chest pain or diarrhoea. Three months ago she developed intermittent, sharp RUQ pains. On physical examination she has a temperature of 38°C, moderate RUQ tenderness on palpation, but no evidence of jaundice.
Task: Applicant should write diagnosis, plan of investigation, carry out differential diagnosis, prescribe treatment for this case history.
3.2. recommendations (instructions) for performing tasks (professional algorithms, orientation maps for the formation of practical skills, etc.)
Professional algorithms.
XVI. Patient's examination.
During patient's examination students should keep such communicative skills:
1. Friendly face expression.
2. Kind voice tone.
3. Greetings, showing concern and respect about the patient.
4. Find out patient's complaints and anamnesis .
5. Explanation of investigation results.
6. Explanation of specific actions (hospitalization, carrying out investigations) which are planned to be performed in the future.
7. Finishing of the talk.
XVII. Patient's examination and investigation algorithm.
1. It should be explained to patient which investigation will be held and indications for this investigation.

2. A doctor should receive patient's agreement on investigation.
3. A doctor should warn patient about possibilities of unpleasant feelings during investigation.
4. Results of investigation should be explained to a patient.
5. Physical examination may reveal right upper quadrant (RUQ) tenderness or a palpable mass. A positive Murphy's sign (the examiner's hand rests along the costal margin and deep inspiration causes pain) has a specificity of 79% to 96% for acute cholecystitis.
6. FBC and C-reactive protein (CRP) should be assessed to look for evidence of an inflammatory process. Liver function tests may show elevated bilirubin, alkaline phosphatase, and gamma-GT.
7. RUQ ultrasound should be the first test ordered and can be performed at the patient's bedside.
8. RUQ ultrasound examination provides anatomical information about gallbladder size, stone size, gallbladder wall, and bile duct size.
9. Abdominal CT scan is inferior to ultrasound in assessing acute biliary disease, but it is useful when obesity or gaseous distension limits ultrasound interpretation. It is also indicated for evaluation of suspected complications (such as abscess) and concurrent intra-abdominal conditions.
10. Cholescintigraphy (hepatobiliary iminodiacetic acid scan) directly shows cystic duct obstruction. The absence of gallbladder filling within 60 minutes after the administration of tracer indicates obstruction of the cystic duct and has a sensitivity of >90% for acute cholecystitis.

XVIII. Step-by-step algorithm of treatment.

1. A patient should informed be about necessity of the prescribed treatment.
2. Dosages, drugs intake regimens, duration of treatment, side effects of the prescribed therapy should be kindly explained to patient.
3. When a diagnosis of cholecystitis is suspected, medical treatment, including NSAIDS, intravenous fluids, antibiotics and analgesia, together with close monitoring of blood pressure, pulse, and urinary output, should be initiated.
4. In mild grade of cholecystitis patients treated with oral antibiotic drugs: second-generation cephalosporin or a combination of a quinolone and metronidazole plus NSAIDS.
5. Early laparoscopic cholecystectomy is considered the primary approach (within 1 week of onset of symptoms).
6. Patients who do not improve under conservative treatment are referred for either surgery or percutaneous cholecystostomy, usually within 1 week of onset of symptoms.
7. If medical management fails, and patients are poor surgical candidates (e.g., medically not fit for surgery), a percutaneous cholecystostomy tube should be considered.
8. Endoscopic transpapillary gallbladder drainage or endoscopic ultrasound-guided gallbladder drainage is considered the first-line alternative to surgical intervention in surgically high-risk patients with acute cholecystitis.
9. Severe (grade III) cholecystitis is defined as organ dysfunction in at least any one of the following organs/systems of cardiovascular (hypotension requiring treatment with dopamine ≥5 micrograms/kg per minute, or any dose of noradrenaline [norepinephrine]), CNS (decreased level of consciousness), respiratory (PaO2/FiO2 ratio 176.8 micromols/L [>2.0 mg/dL]), hepatic (INR >1.5), or haematological (platelet count < 100000 cells/microlitre. These patients need intensive supportive care and urgent cholecystectomy.

3.3. requirements for applicants work results.

As a results of studying applicants must perform the following:
-possess skills of communication and clinical examination of a patient with gallstone disease, chronic cholecystitis and functional biliar diskinesies;
-collect data on patient complaints, medical history, life history;
-evaluate information about the diagnosis of gallstone disease, chronic cholecystitis and functional biliar diskinesies using a standard procedure, based on the results of laboratory and instrumental studies;

-determine the list of required clinical, laboratory and instrumental studies and evaluate their results;
- identify the leading clinical symptom or syndrome;
- establish the most probable or syndrom diagnosis;
-assign laboratory and instrumental investigations for patient;
-carry out differential diagnosis in gallstone disease, chronic cholecystitis and functional biliar diskinesies;
-establish preliminary and clinical diagnosis;
-determine indications for surgical treatment;
- determine the principles of treatment, diet regimen for the patient.

Work 1

1. Collection of complaints, anamnesis, examination of a patients with gallstone disease and chronic cholecystitis.
2. Detection of clinical and instrumental symptoms.
3. Grouping symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data.
6. Carrying out a differential diagnosis.
7. Formulation of the clinical diagnosis.
8. Write a prescription list for patients diagnosed with gallstone disease and chronic cholecystitis, which would include diet and prescribed drugs.
9. Determining of the disability degree.

Work 2.

Assignment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the department library with thematic literature.
The applicant fills in the protocol of the patient's examination. An example of the initial examination of the patient is attached.
The tests for self-control with standard answers.

1. A 60-year-old woman, mother of 6 children, developed a sudden onset of upper abdominal pain radiating to the back, accompanied by nausea, vomiting, fever and chills. Subsequently, she noticed yellow discoloration of her sclera and skin. On physical examination the patient was found to be febrile with temp of 38,9ºC, along with right upper quadrant tenderness. The most likely diagnosis:

A Choledocholithiasis
B Benign biliary stricture
C Malignant biliary stricture
D Carcinoma of the head of the pancreas
E Choledochal cyst

2. A 43 y.o. woman complains of severe pain in the right abdominal side irradiating in the right supraclavicular area, fever, dryness and bitterness in the mouth. There were multiple vomitings without relief. Patient relates the onset of pain to the taking of fat and fried food. Physical examination: the patient lies on the right side, pale, dry tongue, tachycardia. Right side of abdomen is painful during palpation and somewhat tense in right hypochondrium. What is the most likely diagnosis?

A Perforative ulcer
B Acute cholecystitis
C Acute bowel obstruction
D Acute appendicitis
E Right-sided renal colic

3. A 50-year-old patient complains about having pain attacks in the right subcostal area for about a year. He pain arises mainly after taking fattening food. Over the last week the attacks occurred daily and became more painful. On the 3rd day of hospitalization the patient presented with icterus of skin and scleras, light-colored feces and dark urine. In blood: neutrophilic leukocytosis - 13,1X10^9/l, ESR- 28 mm/h. What is the most likely diagnosis?
A Fatty degeneration of liver
B Chronic recurrent pancreatitis
C Chronic calculous cholecystitis
D Chronic cholangitis, exacerbation stage
E Hypertensive dyskinesia of gallbladder
4. A 45 y.o. man has complained of having epigastric and right subcostal aching pain, pruritus, indigestion, dark color of the urine and acholic stool, fever and significant weight loss for 1 month. On examination: jaundice, presence of Curvuasier's sign. US scan did notreveal stones in the gallbladder and choledochus. What is the most likely diagnosis?
A Chronic cholangitis
B Gallbladder stones
C Chronic pancreatitis
D Cancer of the pancreas head
E Chronic hepatitis
5. A 50 year old woman complained of attacks of right subcostal pain after fatty meal she has been suffering from for a year. Last week the attacks repeated every day and became more painful. What diagnostic study would you recommend?
A Blood cell count
B Liver function tests
C X-ray examination of the gastrointestinal tract
D Ultrasound study of the pancreas
E Ultrasound examination of the gallbladder
6. A 60 y.o. woman complains of unbearable pains in the right hypochondrium. In the medical history: acute pancreatitis. Body temperature is 38,2^{0}C. Objectively: icterus sclera. No symptoms of peritoneum irritation are present. There are positive
Ortner's and Hubergrits-Skulski's symptoms. Urine diastase is 320 g/h. What diagnosis is the most probable?
A Chronic pancreatitis
B Acute cholangitis
C Chronic cholecystitis
D Acute cholecystitis
E Cancer of pancreas
Standard answers: 1-A, 2-B, 3-C, 4-D, 5-E, 6-A.
IV. Summarizing, announcing the final grade, announcing the task for the next lesson.
Recommended resources:
- Basic literature source:
1. EASL Clinical Practice Guidelines on the prevention, diagnosis and treatment of gallstones // Journal of Hepatology Journal of Hepatology, 2017.- Vol. 65. – P. 146–181.
2. Gutt C, Schläfer S, Lammert F. The Treatment of Gallstone Disease. Dtsch Arztebl Int. 2020 Feb 28;117(9):148-158. doi: 10.3238/arztebl.2020.0148. PMID: 32234195; PMCID: PMC7132079.
- Additional literature source:
1. American College of Radiology and Society for Pediatric Radiology. ACR-SPR practice parameter for the performance of hepatobiliary scintigraphy. 2017 [internet publication].
https://www.acr.org/-/media/ACR/Files/Practice-Parameters/hepato-scint.pdf?la=en
2. Meeralam Y, Al-Shammari K, Yaghoobi M. Diagnostic accuracy of EUS compared with MRCP in detecting choledocholithiasis: a meta-analysis of diagnostic test accuracy in head-to-head studies. *Gastrointest Endosc.* 2017;86:986–993.

Appendix 1

Example of the primary examination of the patient

Passport data: name and surname, age

Complaints:

Constant, dull pain in the right hypochondrium, nausea, bitter taste in the mouth, constipation up to 4-5 days.

Anamnesis morbi

Ill for about a year. Previously, he did not look for medical help and wasn't examined.

Anamnesis vitae

Living conditions are satisfactory. Botkin's disease, tuberculosis, sexually transmitted diseases, malaria denies.

Professional anamnesis: not burdened.

Hereditary history is not burdened.

Pave not been in contact with infectious patients for the last 3 days. He has not left the country in the last 3 years.

***Hereditary history**: not burdened*

Neurological history

At the time of examination signs of focal neurological symptoms were not detected.

***Allergic history**: not burdened*

Epidemiology

Tuberculosis, malaria, viral hepatitis, Botkin's disease, veneral disease, HIV, AIDS, pediculosis – denies.

***Oncoanamnesis**: denies.*

***Insurance anamnesis**: There is no need to issue a seak leave, for the last 12 months a seak leave document has not been issued in this regard.*

***Postponed operations**: denies.*

***Bad habits**: denies.*

Examination of organ systems:

GENERAL Condition: satisfactory

CONSCIOUSNESS: clear

Body shape: hypostenic

Fatness: low nutrition

POSITION OF THE PATIENT: active

BODY TEMPERATURE: 36.6 C. Signs of alcohol intoxication - no

SKIN: Skin of pale color, clean. Tissue turgor is normal. Skin pigmentation: depigmentation - no. Rash: no; other changes in the skin: no.

Visible mucous membranes: Normal color

LYMPH NODES: not enlarged

THYROID GLAND: no pathology

Oncological examination was performed, no visual forms of oncopathology were detected

Cardiovascular system:

PERCUSSION OF THE HEART: the limits of relative cardiac dullness: right on the right edge of the sternum, upper -III rib on the left parasternalis line, left - 1 cm outward from the left mediaclavicularis line in the V intercostal space

HEART activity: rhythmic, heart rate - 74 per 1 min. Pulse 74 in 1 min. Heart tones: muffled

HEART MURMURS: no

EDEMA: no

BP 125 / 85 mm Hg

EXAMINATION OF ARTERIES: no pathology

VEIN STUDY: no pathology

RESPIRATORY SYSTEM:

BREATHING: no dyspnea at rest, RR 16 in 1 min.

Sputum: no
CHEST: cylindrical, not deformed. Intercostal spaces: NOT smoothed. Participation of additional muscles: no, RR – 16 in 1 min. SpO2 = 98%
Percussion over the lungs: clear lung sound.
PULMONARY AUSCULTATION: vesicular breathing over both lungs. Pleural friction noise - no
DIGESTIVE SYSTEM:
TONGUE: wet; covered with grey plaque.
Tonsils: not enlarged
STOMACH: participates in the act of breathing. No hernia. Pulsation in the epigastrium - no. There is no dilation of the subcutaneous veins
Palpation: moderate pain in the right hypohondrium at the point of projection of the gallbladder - the point of crossection of the outer edge of the musculus rectus abdominis with the right costal arch. A positive Kerr's symptom - pain in palpation on inspiration at the point of projection of the gallbladder. A positive Ortner's symptom - pain when stabbing on the edge of the right costal arch. Positive Mussi-Georgievsky (phrenicus symptom) symptom - pain on palpation between the legs of the musculus sternocleidomastoideus on the right side. The pain radiates downward.
Pathological symptoms: not detected
Liver: not enlarged
Gallbladder: not palpable
Pancreas: painless
Spleen: not palpable,
PERCUTIONAL SOUND OVER THE ABDOMINAL CAVITY: unchanged,
FECES: normal, no pathological impurities
URINARY SYSTEM:
Palpation of the kidneys: not palpable
Pasternatsky's symptom is negative on both sides.
Urination: free, painless, frequency per day: 3-4 times.
Urinary incontinence: no.
SENSES:
SIGHT: not violated (OU). There is no other pathology
HEARING: normal, no deafness, pain: no. Tinnitus: no.
Musculoskeletal system:
Pathology of the musculoskeletal system was not detected
On the basis of complaints, anamnesis, objective examination, it is possible to make a preliminary diagnosis:
Functional biliary disorder of hypotonic-hypokinetic type.
Plan of investigation
general blood test, general urine test, glycemia level (8.00, 13.00, 17.00, 21.00).
Biochemistry: liver tests - total bilirubin and fractions, ALT, AST, glucose, protein, lipid spectrum, coagulogram, amylase, AF, LDH, GGT, CPK, serum iron, CRP, electrolytes (potassium, sodium, calcium, chloride), antibodieas for viral hepatitis, feces test.
ECG, ultrasound of abdomen, ultrasound of the gallbladder with a test breakfast, duodenal probe, FGDS, cholecystography,
Consultation of gastroenterologist.
Treatment plan
Diet.
Drug therapy:
- Hofitol - 2 tab. x 3 times a day, 30 minutes before meal
- Ursofalk - 250 mg - 3 tablets at night for 2-3 months
- Motilium 10 mg - 1 tab. x 3 times a day, 30 minutes before meal

Appendix 2

Tests of basic knowledge level in KROK format

Theme 23. Gallstone disease. Chronic cholecystitis and functional biliar diskenesias.

1. A patient 48 y.o., complains of dull pain in a right hypochondrium after meal, especially fatty, fried, smoked. Considers himself a sick person for 12 years. During objective exmination abdomen is slightly bloated, painful in a right hypochondrium. Liver at the edge of a costal margin, painfless. Spleen isn't palpable. Positive symptoms of Kehr, Murphy, Ortner are found. What disease should one think of?
A. Ulcerative disease of a duodenum, active phase.
B. Chronic pancreatitis in phase of exacerbation.
C. Chronic gastritis in phase of exacerbation.
D. Chronic cholecystitis in phase of remission.
E. Chronic cholecystitis in phase of exacerbation.
2. A patient 38 y.old, had US of a gallbladder whose walls are thickened, echogenicity is increasd, double-contour of a gallbladder in a lumen – biliary sludge. What are these changes evidence of?
A. Hypermotor dyskinesia of a gallbladder.
B. Hypomotor dyskinesia of a gallbladder.
C. Chronic inflammation of a gallbladder.
D. Tumour of a gallbladder.
E. Empyema of a gallbladder.
3. A patient had the following results during US of organs of abdominal cavity: gallbladder isn't enlarged. Echo suspension is detected. A chronic cholecystitis is supected. What disease should the differential diagnostics is done with?
A. Gallbladder empyema.
B. Tumour of a gallbladder.
C. Cholelithiasis.
D. Hydrops of gallbladder.
E. Cholesterosis of a gallbladder.
4. A patient 37 y.old, has diagnosis: chronic noncalculous cholecystitis with geneticaly-hypertonic dyskinesia of a gallbladder. What group of medicines should be indicated for this patient?
A. Blockers of H2-histamine receptors.
B. Proton pumps inhibitors.
C. Enzymatic drugs.
D. Myotropic spasmolytics.
E. Cholekinetics.
5. A patient has a chronic noncalculous cholecystitis in the phase of exacerbation. Complains with intensive pain in a right hypochondrium, nausea, vomiting, rise of temperature to 38,5^{0}C. Blood: leukocytes — 18 G/l,stab— 15%, ESR — 30 мм/h; total bilirubin — 22 мсmol/l, direct bilirubim — 4,2 мсmol/l. Development of what disease of a patient can be suspected?
A. Gangrene of a gallbladder.
B. Obstructive jaundice.
B. Chronic hepatitis.
D. Gallbladder empyema.
E. Chronic pancreatitis.
6. A 50 year old woman complained of attacks of right subcostal pain after fatty meal she has been suffering from for a year. Last week the attacks repeated every day and became more painful. What diagnostic study would you recommend?
A. Ultrasound examination of the gallbladder
B. Liver function tests
C. X-ray examination of the gastrointestinal tract

D. Ultrasound study of the pancreas
E. Blood cell count
7. A 60-year-old woman, mother of 6 children, developed a sudden onset of upper abdominal pain radiating to the back, accompanied by nausea, vomiting, fever and chills. Subsequently, she noticed yellow discoloration of her sclera and skin. On physical examination the patient was found to be febrile with T 38,9ºC, along with right upper quadrant tenderness. The most likely diagnosis is:
A. Choledocholithiasis
B. Benign biliary stricture
C. Malignant biliary stricture
D. Carcinoma of the head of the pancreas
E. Choledochal cyst
8. The complications of acute cholecystitis which require surgical intervention are as follows EXCEPT:
A. Jaundice
B. Empyema of the gall-bladder
C. Emphysematous gall-bladder
D. Gall-bladder perforation
E. Cholangitis conditioned by the presence of stones in the bile tract
9. A 37-year-old patient has sudden acute pain in the right epigastric area after having fatty food. What method of radiological investigation is to be used on the first stage of examining the patient?
A. Ultrasonic
B. Roentgenological
C. Radionuclid
D. Magnetic-resonance
E. Thermographic
10.A 50-year-old patient complains about having pain attacks in the right subcostal area for about a year. He pain arises mainly after taking fattening food. Over the last week the attacks occurred daily and became more painful. On the 3rd day of hospitalization the patient presented with icteritiousness of skin and scleras, light-colored feces and dark urine. In blood: neutrophilic leukocytosis -13,1*10^9, ESR- 28 mm/h. What is the most likely diagnosis?
A. Chronic calculous cholecystitis
B. Chronic recurrent pancreatitis
C. Fatty degeneration of liver
D. Chronic cholangitis, exacerbation stage
E. Hypertensive dyskinesia of gallbladder

Practical lesson #24

1. Theme: Chronic hepatitis

2. Goal:

To study:

- chronic hepatitis: definition;
- etiology, pathogenesis of chronic hepatitis;
- chronic hepatitis: classification;
- clinic manifestations of chronic hepatitis;
- diagnosis and differential diagnosis;
- treatment strategies for different types of hepatitis;
- complications of chronic hepatitis.

3. Basic concepts. Chronic hepatitis: definition, aetiology, pathogenesis. Classification. Diagnostics and differential diagnostics. Treatment. Complications. Prognosis.

Chronic hepatitis is hepatitis that lasts > 6 mo. Common causes include hepatitis B and C viruses, autoimmune mechanisms (autoimmune hepatitis), and drugs. 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 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 end-stage disease.

Etiology

Hepatitis lasting > 6 mo is generally defined as chronic, although this duration is arbitrary. 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. Hepatitis A and E viruses are not causes. Although the mechanism of chronicity is uncertain, liver injury is mostly determined by the patient's immune reaction to the infection.

Many cases are idiopathic. A high proportion of idiopathic cases have prominent features of immune-mediated hepatocellular injury (autoimmune hepatitis), including the following:

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

Sometimes chronic hepatitis has features of both autoimmune hepatitis and another chronic liver disorder (eg, primary biliary cirrhosis, chronic viral hepatitis). These conditions are called overlap syndromes.

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

Other causes of chronic hepatitis include alcoholic hepatitis and nonalcoholic steatohepatitis. Less often, chronic hepatitis results from α_1-antitrypsin deficiency, celiac disease, a thyroid disorder, or Wilson disease.

Cases were once classified histologically as chronic persistent, chronic lobular, or chronic active hepatitis. A more useful recent classification system specifies the etiology, the intensity of

histologic inflammation and necrosis (grade), and the degree of histologic fibrosis (stage). Inflammation and necrosis are potentially reversible; fibrosis usually is not.

Symptoms and Signs

Clinical features vary widely. About one third of cases develop after acute hepatitis, but most develop insidiously de novo. Many patients are asymptomatic, especially in chronic HCV infection. However, malaise, anorexia, and fatigue are common, sometimes with low-grade fever and nonspecific upper abdominal discomfort. Jaundice is usually absent. Often, particularly with HCV, the first findings are signs of chronic liver disease (eg, splenomegaly, spider nevi, palmar erythema). 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 HCV is occasionally associated with lichen planus, mucocutaneous vasculitis, glomerulonephritis, porphyria cutanea tarda, and, perhaps, non-Hodgkin B-cell lymphoma. About 1% of patients develop symptomatic cryoglobulinemia with fatigue, myalgias, arthralgias, neuropathy, glomerulonephritis, and rashes (urticaria, purpura, or leukocytoclastic vasculitis); asymptomatic cryoglobulinemia is more common.

Diagnosis

- ✓ Liver function test results compatible with hepatitis
- ✓ Viral serologic tests
- ✓ Possibly autoantibodies, immunoglobulins, α_1-antitrypsin level, and other tests
- ✓ Usually biopsy
- ✓ Serum albumin, platelet count, and PT

The diagnosis is suspected in patients with suggestive symptoms and signs, incidentally noted elevations in aminotransferase levels, or previously diagnosed acute hepatitis. In addition, to identify asymptomatic patients, the CDC recommends testing all people born between 1945 and 1965 once for hepatitis C. Liver function tests are needed if not previously done and include serum ALT, AST, alkaline phosphatase, and bilirubin. Aminotransferase elevations are the most characteristic laboratory abnormalities. Although levels can vary, they are typically 100 to 500 IU/L. ALT is usually higher than AST. Aminotransferase levels can be normal during chronic hepatitis if the disease is quiescent, particularly with HCV. Alkaline phosphatase is usually normal or only slightly elevated but is occasionally markedly high. Bilirubin is usually normal unless the disease is severe or advanced. However, abnormalities in these laboratory tests are not specific and can result from other disorders, such as alcoholic liver disease, recrudescent acute viral hepatitis, and primary biliary cirrhosis.

If laboratory results are compatible with hepatitis, viral serologic tests are done to exclude HBV and HCV.

Hepatitis B Serology

Marker	**Acute HBV Infection**	**Chronic HBV Infection**	**Prior HBV Infection**[†]
HBsAg	+	+	–
Anti-HBs	–	–	+[‡]
IgM anti-HBc	+	–	–
IgG anti-HBc	–	+	±
HBeAg	±	±	–
Anti-HBe	–	±	±
HBV-DNA	+	+	–
*Antibody to hepatitis D virus (anti-HDV) levels should be measured if serologic tests confirm HBV and infection is severe.			
[†]Patients have had HBV infection and recovered.			
[‡]Anti-HBs is also seen as the sole serologic marker after HBV vaccination.			
Anti-HBc = antibody to hepatitis B core; anti-HBe = antibody to HBeAg; anti-HBs = antibody to			

HBsAg; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus.

Hepatitis C Serology

Marker	Acute HCV Infection	Chronic HCV Infection	Prior HCV Infection*
Anti-HCV	+	+	+
HCV-RNA	+	+	–
*Patients have had HCV infection and spontaneously recovered or been successfully treated.			
Anti-HCV = antibody to HCV; HCV = hepatitis C virus.			

Unless these tests indicate viral etiology, further testing is required. The first tests done include autoantibodies, immunoglobulins, thyroid tests (thyroid-stimulating hormone), tests for celiac disease (tissue transglutaminase antibody), and α_1-antitrypsin level. Children and young adults are screened for Wilson disease by measuring the ceruloplasmin level. Marked elevations in serum immunoglobulins suggest chronic autoimmune hepatitis but are not conclusive. Autoimmune hepatitis is normally diagnosed based on the presence of antinuclear (ANA), anti–smooth muscle, or anti-liver/kidney microsomal type 1 (anti-LKM1) antibodies at titers of 1:80 (in adults) or 1:20 (in children).

Unlike in acute hepatitis, biopsy is necessary. 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.

In most cases, the specific cause of chronic hepatitis cannot be discerned via biopsy alone, although cases caused by HBV can be distinguished by the presence of ground-glass hepatocytes and special stains for HBV components. Autoimmune cases usually have a more pronounced infiltration by lymphocytes and plasma cells. In patients with histologic but not serologic criteria for chronic autoimmune hepatitis, variant autoimmune hepatitis is diagnosed; many have overlap syndromes.

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

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 should be screened every 6 to 12 mo for hepatocellular cancer with ultrasonography and serum α-fetoprotein measurement, although the cost-effectiveness of this practice is debated. Patients with chronic HCV infection should be similarly screened only if cirrhosis is present.

Prognosis

Prognosis is highly variable. 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. Untreated chronic hepatitis due to HCV causes cirrhosis in 20 to 30% of patients, although development may take decades. Chronic autoimmune hepatitis usually responds to therapy but sometimes causes progressive fibrosis and eventual cirrhosis.

Chronic HBV infection increases the risk of hepatocellular cancer. The risk is also increased in chronic HCV infection, but only if cirrhosis has already developed.

Treatment

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

Treatment goals include treating the cause and managing complications (eg, ascites, encephalopathy). Drugs that cause hepatitis should be stopped. Underlying disorders, such as Wilson disease, should be treated. 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 require treatment with corticosteroids, immunosuppressive therapies, or cytotoxic chemotherapy for other disorders, they should be treated with antiviral drugs at the same time to prevent a flare-up of acute hepatitis B and acute liver failure due to hepatitis B.

Autoimmune hepatitis:

Corticosteroids, with or withoutazathioprine, prolong survival. Prednisoneis usually started at 30 to 60 mg po once/day, then tapered to the lowest dose that maintains aminotransferases at normal or near-normal levels. Some experts give concomitant azathioprine1 to 1.5 mg/kg po once/day; others add azathioprine

only if low-dose prednisonefails to maintain suppression. Most patients require long-term, low-dose maintenance treatment. Liver transplantation may be required for end-stage disease.

HBV:

Antiviral treatment is indicated for patients with elevated aminotransferase levels, clinical or biopsy evidence of progressive disease, or both. The goal is to eliminate HBV-DNA. Treatment may need to be continued indefinitely and thus may be very expensive; stopping treatment prematurely can lead to relapse, which may be severe. However, treatment may be stopped if HBeAg converts to anti-HBe or if tests for hepatitis B surface antigen (HBsAg) become negative. Drug resistance is also a concern. Seven antiviral drugs—entecavir, adefovir, lamivudine, interferon alfa (INF-α), pegylated INF-α (peginterferon-α), telbivudine, and tenofovir—are available.

First-line treatment is usually with an oral antiviral drug, such as entecavir(a nucleoside analog) ortenofovir(a nucleotide analog). Oral antiviral drugs have few adverse effects and can be given to patients with decompensated liver disease. Combination therapy has not proved superior to monotherapy, but studies continue to examine their comparative usefulness. HBsAg becomes undetectable and HBeAg seroconversion occurs in patients with HBeAg-positive chronic HBV infection; these patients may be able to stop antiviral drugs. Patients with HBeAg-negative chronic HBV infection almost always need to take antiviral drugs indefinitely to maintain viral suppression; they have already developed antibodies to HBeAg, and thus the only specific criterion for stopping HBV treatment would be HBsAg that becomes undetectable.

Entecavirhas a high antiviral potency, and resistance to it is uncommon; it is considered a first-line treatment for HBV infection. Entecaviris effective against adefovir-resistant strains. Dosage is 0.5 mg po once/day; however, patients who have previously taken a nucleoside analog should take 1 mg po once/day. Dose reduction is required in patients with renal insufficiency. Serious adverse effects appear to be uncommon, although safety in pregnancy has not been established.

Tenofovirhas replaced adefovir(an older nucleotide analog) as a first-line treatment. Tenofoviris the most potent oral antiviral for hepatitis B; resistance to it is minimal. Dosage is 300 mg po once/day; dosing frequency may need to be reduced if creatinine clearance is reduced.

For adefovir, dosage is 10 mg po once/day.

Interferon alfa (IFN-α) can be used but is no longer considered first-line treatment. Dosage is 5 million IU sc once/day or 10 million IU sc 3 times/wk for 16 to 24 wk in patients with HBeAg-positive chronic HBV infection and for 12 to 24 mo in patients with HBeAg-negative chronic HBV infection. In about 40% of patients, this regimen eliminates HBV-DNA and causes seroconversion

to anti-HBe; a successful response is usually presaged by a temporary increase in aminotransferase levels. The drug must be given by injection and is often poorly tolerated. The first 1 or 2 doses cause an influenza-like syndrome. Later, fatigue, malaise, depression, bone marrow suppression, and, rarely, bacterial infections or autoimmune disorders can occur. In patients with advanced cirrhosis, IFN-α can precipitate liver failure and is therefore contraindicated. Other contraindications include renal failure, immunosuppression, solid organ transplantation, and cytopenia. In a few patients, treatment must be stopped because of intolerable adverse effects. The drug should be given cautiously or not at all to patients with ongoing substance abuse or a major psychiatric disorder. Pegylated IFN-α can be used instead of IFN-α. Dosage is usually 180 mcg by injection once/wk for 48 wk. Adverse effects are similar to those of IFN-α but may be less severe.

Lamivudine(a nucleoside analog) is no longer considered first-line treatment for HBV infection because risk of resistance is higher and efficacy is lower than those of newer antiviral drugs. Dosage is 100 mg po once/day; it has few adverse effects.

Telbivudine is a newer nucleoside analog that has greater efficacy and potency than lamivudinebut also has a high rate of resistance; it is not considered first-line treatment.

Liver transplantation should be considered for end-stage liver disease caused by HBV. In patients with HBV infection, the long-term use of first-line oral antivirals and peritransplantation use of hepatitis B immune globulin(HBIG) has improved outcomes after liver transplantation. Survival is equal to or better than that after transplantation for other indications, and recurrences of hepatitis B are minimized.

HCV:

For chronic hepatitis due to HCV, treatment is indicated if aminotransferase levels are elevated and biopsy shows active inflammatory disease with evolving fibrosis. The goal of treatment is permanent elimination HCV-RNA (sustained virologic response), which is associated with permanent normalization of aminotransferase and cessation of histologic progression. Treatment results are more favorable in patients with moderate fibrosis and a viral load of < 600,000 to 800,000 IU/mL than in patients with cirrhosis and a viral load of > 800,000 IU/mL.

HCV genotype is determined before treatment because genotype influences the course, duration, and success of treatment. Genotype 1 is more common than genotypes 2, 3, and 4; it accounts for 70 to 80% of cases of chronic hepatitis C in the US.

Patients with all genotypes are treated with pegylated IFN-α plus ribavirin(dual therapy—see below). Patients with genotype 1 are also given a protease inhibitor. New treatment regimens are emerging, but not yet ready for general clinical use. Some include use of sofosbuvir, particularly for patients infected with HCV genotypes 2 or 3 (and are thus not eligible for treatment with protease inhibitors) or who have contraindications to, or have failed treatment with, interferon-based regimens.

Decompensated cirrhosis due to hepatitis C is the most common indication for liver transplantation in the US. HCV recurs almost universally in the graft, and both patient and graft survival are less favorable than when transplantation is done for other indications.

HCV genotype 1:

Genotype 1 is more resistant to treatment with dual therapy with pegylated IFN-α plus ribavirinthan other genotypes. Adding a protease inhibitor (telaprevir or boceprevir) to pegylated IFN-α plus ribavirin increases the rate of sustained virologic response from < 50% (with dual therapy) to 70 to 80%.

Pegylated IFN-α2b 1.5 mcg/kg sc once/wk and pegylated IFN-α2a 180 mcg sc once/wk have comparable results. Adverse effects of pegylated IFN-α are similar to those of IFN-α but may be less severe; contraindications are also similar (see above).

For ribavirin, dosage is 500 to 600 mg po bid,. Ribavirinis usually well-tolerated but commonly causes anemia due to hemolysis; dosage should be decreased if hemoglobin decreases to < 10 g/dL.Ribavirin is teratogenic in both men and women, requiring contraception during treatment and for 6 mo after treatment is completed. Patients who cannot tolerate ribavirin should still be given

pegylated IFN-α, but not using ribavirinreduces the likelihood of successful treatment. Ribavirinmonotherapy is of no value.

If telaprevir is the protease inhibitor chosen, it is given at a dose of 750 mg po tid for 12 wk. The HCV-RNA level should be measured 4 and 12 wk after beginning treatment. If HCV-RNA is undetectable at 4 and 12 wk, triple therapy is followed by another 12 wk of dual therapy with pegylated IFN-α andribavirin(total treatment duration of 24 wk). However, dual therapy should be continued for 36 wk after triple therapy (total treatment duration of 48 wk) if patients have the following:

- ✓ No response to previous antiviral therapies (HCV-RNA did not decrease by at least 2 log levels after treatment for 12 wk) or an incomplete response (called partial responders)
- ✓ HCV-RNA that is detectable at 4 or 12 wk after beginning triple therapy
- ✓ Compensated cirrhosis

If boceprevir is chosen, it is always given at 800 mg po tid, beginning 4 wk after starting dual therapy with pegylated IFN-α plus ribavirin. The HCV-RNA level should be measured at 4, 8, 12, and 24 wk after beginning treatment. If HCV-RNA is undetectable at 8 and 24 wk, triple therapy is given for 24 wk (total treatment duration of 28 wk). In certain cases, treatment duration is increased, as follows:

- If patients responded only partially to previous antiviral therapy and have no detectable HCV-RNA at 8 or 24 wk: 32 wk of triple therapy (total treatment duration of 36 wk)
- If patients have detectable HCV-RNA at 8 wk: 32 wk of triple therapy, followed by 12 wk of dual therapy (treatment duration of 48 wk)
- If patients have detectable HCV-RNA at 4 wk and are tolerating triple therapy: 44 wk of triple therapy (total treatment duration of 48 wk)
- If patients have not responded to previous antiviral therapy or have compensated cirrhosis: 44 wk of triple therapy (total treatment duration of 48 wk)

Telaprevir and boceprevir can cause anemia. Telaprevir can also cause rashes. Both drugs can result in numerous drug-drug interactions.

HCV genotypes 2, 3, and 4:

Dual therapy with pegylated IFN-α plus ribavirinis given. For ribavirin, a dosage of 400 mg po bid may be sufficient for genotypes 2 and 3, but the dosage should be 500 to 600 mg po bid for genotype 4.

For genotypes 2 and 3, treatment is required for only 24 wk, resulting in an overall sustained virologic response in about 75% of patients. Longer treatment does not improve the results. For genotype 4, treatment is given for 48 wk, resulting in a sustained virologic response in 45 to 55% of patients.

Key Points

- Chronic hepatitis is usually not preceded by acute hepatitis and is often asymptomatic.
- If liver function 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, α_1-antitrypsin level) for other forms of hepatitis.
- Do a liver biopsy to confirm the diagnosis and assess the severity of chronic hepatitis.
- Treat autoimmune hepatitis with corticosteroids and sometimes azathioprine.
- Consider entecavirand tenofovir as potential first-line therapies for chronic hepatitis B.
- Treat chronic hepatitis C with pegylated IFN-α plus ribavirin plus, for genotype 1 strains, telaprevir or boceprevir.

4. **Equipment:** study room, ultrasound system “Mylab Six CristaLine”. Students acknowledge with protocol and procedure of liver and biliary tract investigation, visit functional department (1st floor in University Clinic). Results of these investigations are provided to applicants during lesson.
5. **Learning hours:** 4 hours.

Plan of the lesson

I. Organizational moment (greetings, checking who is present on the lesson, announcing topic and goal of the lesson, motivating applicants to study the topic).

II. Control of basic knowledge (oral questioning, tests, checking of how clinical cases and workbooks are fulfilled).

2.1. Demands for applicants theoretical preparation

Applicants should know.

Didactic units list:

1. Chronic hepatitis: definition.
2. Etiology, pathogenesis.
3. Classification of different types of hepatitis.
4. Clinical features of each type.
5. Criteria of diagnostics.
6. Differential diagnosis.
7. Complications of chronic hepatitis.
8. Treatment approaches and strategies.
9. Primary and secondary prophylaxis.
10. Prognosis for life, convalescence and work capacity.

Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Tests for self-control

1. Patient suffering from a chronic viral C hepatitis, complains of a significant cutaneous itching. What's the pathogenesis of this complaint?

A. Allergy.
B. Neurasthenia.
C. Cholestasis.+
D. Intoxication.
E. Portal systemic encephalopathy.

2. Patient K. complains of heaviness, dull nagging pains in the right hypochondrium, increasing after physical exertion, having no clear connection with taking of food. No attacks of intensive pains in abdomen. General weakness, cutaneous itching, periodical icteritiousness of skin. What disease is the most probable?

A. Chronic acalculous cholecystitis.
B. Chronic pancreatitis.
C. Chronic hepatitis. +
D. Hemolytic anemia.
E. Chronic calculous cholecystitis.

3. 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 mcmol/L, AST- 2,1 mmol/L, ALT- 1,8 mmol/L, alkaline phosphatase - 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

4. 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 mkmol/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
5. A 40-year-old man is ill with autoimmune hepatitis. Blood test: IgA/G ratio 0,8, bilirubin - mcmol/l, transaminase : ALT- 73 U/l, AST – 52 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
6. Patient B., 38 years, has been abusing alcohol for half a year. During palpation a moderate liver enlargement is detected, spleen is not enlarged. No free fluid in the abdominal cavity. During a biochemical analysis of blood there is: ALT, AST, bilirubin, blood triglycerides — normal; insignificant increase of γ-glutamiltranspeptidase. During sonography — moderate enlargement of liver, structure is homogeneous, increased echogenicity. Your diagnosis?
A. Chronic alcoholic hepatitis with minimal activity.
B. Fatty hepatosis of alcohol etiology. +
C. Alcocholic liver cirrhosis.
D. Nonspecific reactive hepatitis.
E. Liver amyloidosis.
7. Patient's illness was diagnosed as a chronic hepatitis with manifestations of cholestasis with a mild activity. Which of the prescriptions is indicated for the patient?
A. Choleretics.
B. Glucocorticoids.
C. Vitamins.
D. Ursodeoxycholic acid. +
E. Hepatoprotectors based on phospholipids.
8. Patient G. is suspected of having transition of a chronic hepatitis into hepatic cirrhosis. This suspicion could be based on:
A. Detection of positive markers of hepatitis C virus.
B. Detection of bilirubinemia.
C. Detection of hypercholesterolemia.
D. Detection of diffuse changes of the liver at sonography.+
E. Detection of esophageal varicose veins dilatation.
9. Patient C. has a chronic hepatitis. What pain characteristic is more typical of this disease?
A. Cramping pains in the right part of abdomen.
B. Stinging pains in the right hypochondrium.
C. Compressing pains in epigastric region and right hypochondrium.
D. Nagging pains, heaviness in the right hypochondrium. +
E. Burning sensation in the upper part of abdomen.
10.Patient R. has alcoholic cirrhosis of the liver with significant portal hypertension. Choose the medicine for treatment of a portal hypertension.
A. Verospiron. +
B. Sulfanilamide.
C. Medicines of a nitrofuran range.
D. Glucocorticosteroids.
E. Hepatoprotectors.

III. Formation of professional skills, abilities:
3.1. content of tasks (tasks, clinical situations, etc.)

Case history #1
A 40-year-old asymptomatic man presents for a routine visit with elevated alanine aminotransferase (ALT) level (55 international units [IU]/mL). His mother died of hepatocellular carcinoma and he has a middle-aged sister with "hepatitis B infection". He has a normal physical examination and has no stigmata of chronic liver disease.
Case history #2
A 38-year-old man presents to the emergency department for severe alcohol abuse with nausea and vomiting. He has a significant medical history of chronic heavy alcohol consumption of about one bottle of wine each day for about 5 years until 1 year ago; since then he has had severe intermittent binge alcohol intake. He reports no other significant medical problems. The patient is confused and slightly obtunded, and hepatomegaly is discovered on physical exam. His body mass index is 22. Pertinent positive laboratory values show low haemoglobin, AST elevation > ALT elevation, normal PT and INR, and very high serum alcohol level. Ultrasound of the abdomen shows fatty infiltration in the liver.

Case history #3
A 42-year-old man is referred to the liver clinic with mild elevation in aminotransferases for several years. He has a medical history significant for obesity, hypertension, and hypercholesterolaemia. He does not smoke or drink alcohol and there is no high-risk behaviour. He has a family history of premature cardiac disease. He is taking a diuretic and, because of his elevated liver tests, was recommended to discontinue his statin medication several months ago. Other than complaints of mild fatigue, the patient feels well. Examination is notable for a BMI of 37 kg/m², truncal obesity, and mild hepatomegaly.

Task: Applicant should write diagnosis, plan of investigation, carry out differential diagnosis, prescribe treatment for these case histories.

3.2. recommendations (instructions) for performing tasks (professional algorithms, orientation maps for the formation of practical skills, etc.)

Professional algorithms.

XIX. Patient's examination.

During patient's examination students should keep such communicative skills:
1. Friendly face expression.
2. Kind voice tone.
3. Greetings, showing concern and respect about the patient.
4. Find out patient's complaints and anamnesis .
5. Explanation of specific actions (hospitalization, carrying out investigations) which are planned to be performed in the future.
6. Student should perform liver palpation and percussion.
7. Finishing of the talk.

XX. Patient's investigation algorithm.

1. It should be explained to patient which investigation will be held and indications for this investigation.
2. A doctor should receive patient's agreement on investigation.
3. A doctor should warn patient about possibilities of unpleasant feelings during investigation.
4. Results of investigation should be explained to a patient.
5. Liver function test should be done: check of ALT, AST, AP, GGT, Bilirubin, Total protein, Albumin values.

6. Serum HBeAg, HBV DNA, serum anti-HBe, HBV and HCV genotype, anti-HCV antibodies, HCV RNA should be checked.
7. Urea, electrolytes, ammonia level and folate should be checked.
8. Iron studies (for haemochromatosis) and copper studies (for Wilson's disease) should be done.
9. Total cholesterol, LDL, triglyceride, and low HDL should be checked.
10. Anti-nuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) (for autoimmune hepatitis) should be checked.
11. Anti-soluble liver antigens or liver/pancreas (anti-SLA/LP) are highly specific markers of autoimmune hepatitis.
12. Antibodies to liver/kidney microsome type 1 antigen (anti-LKM-1 antibodies) are characteristic serological marker for the diagnosis of type 2 type of autoimmune hepatitis.
13. Fasting insulin should be measured in all non-diabetic patients with non-alcoholic fatty liver disease or non-alcoholic steatohepatitis regardless of BMI.
14. Coagulation profile should be determined.
15. Gamma-globulin levels should be checked.
16. Cytokeratin-18 fragments - biomarkers may be able to detect the degree of liver injury without the need for liver biopsy.
17. Liver ultrasound should be done.
18. Liver biopsy is used to assess the degree of liver damage and/or fibrosis and to rule out causes of liver disease.
19. Alpha Fetoprotein level is used for screening for hepatocellular carcinoma in conjunction with ultrasound every 6 to 12 months in high-risk HBV carriers.
20. Phases of chronic hepatitis B infection.
21. Non-invasive tests of liver fibrosis (fibromarkers in serum and transient elastography that uses ultrasound and low-frequency waves to measure liver elasticity) may be able to suggest or to exclude advanced fibrosis.

XXI. Step-by-step algorithm of treatment.

1. A patient should informed be about necessity of the prescribed treatment.
2. Dosages, drugs intake regimens, duration of treatment, side effects of the prescribed therapy should be kindly explained to patient.
3. American Association for the Study of Liver Diseases recommendations for treatment regimens in HCV:

• Daclatasvir plus sofosbuvir
• Elbasvir/grazoprevir
• Glecaprevir/pibrentasvir
• Ledipasvir/sofosbuvir
• Ombitasvir/paritaprevir/ritonavir ± dasabuvir
• Sofosbuvir plus simeprevir
• Sofosbuvir/velpatasvir
• Sofosbuvir/velpatasvir/voxilaprevir.

1. There are several agents currently approved for the treatment of chronic HBV: interferon alfa 2b, peginterferon alfa 2a, and the nucleoside/nucleotide analogues. The nucleoside analogues are entecavir and lamivudine. The nucleotide analogues are tenofovir disoproxil and adefovir. The preferred first-line single drug choices are entecavir, peginterferon alfa-2a, and tenofovir disoproxil.
2. In fatty liver hepatitis Orlistat can be used. It is an enteric lipase inhibitor that prevents the absorption of fats from the gastrointestinal tract.
3. Systematic reviews have found that thiazolidinediones (pioglitazone, rosiglitazone) improve liver histological scores in patients with non-alcoholic fatty liver disease (NAFLD).
4. Atorvastatin and antioxidants (vitamins C and E) reduce the odds of hepatic steatosis in patients with hepatic steatosis.

5. In patients with autoimmune hepatitis regimen of prednisone/prednisolone plus azathioprine as an initial treatment option.
6. Mycophenolate and ciclosporin may be considered as alternative immunosuppressants to azathioprine for patients who are intolerant to azathioprine in patients with autoimmune hepatitis.

3.3. requirements for applicants work results.
As a results of studying students must perform the following:
-possess skills of communication and clinical examination of a patient with chronic hepatitis;
-collect data on patient complaints, medical history, life history;
-evaluate information about the diagnosis of chronic hepatitis using a standard procedure, based on the results of laboratory and instrumental studies;
-determine the list of required clinical, laboratory and instrumental studies and evaluate their results;
- identify the leading clinical symptom or syndrome;
- establish the most probable or syndrom diagnosis;
-assign laboratory and instrumental investigations for patient;
-carry out differential diagnosis in different types of chronic hepatitis;
-establish preliminary and clinical diagnosis;
- determine the principles of treatment, diet regimen for the patient.
a. control materials for the final stage of the lesson.

Work 1

1. Collection of complaints, anamnesis, examination of a patients with chronic hepatitis.
2. Detection of clinical and instrumental symptoms.
3. Grouping symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data.
6. Carrying out a differential diagnosis.
7. Formulation of the clinical diagnosis.
8. Write a prescription list for patients diagnosed with chronic hepatitis, which would include diet and prescribed drugs.
9. Determining of the disability degree.

Work 2.

Assignment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the department library with thematic literature.
The student fills in the protocol of the patient's examination. An example of the initial examination of the patient is attached.
The tests for self-control with standard answers.
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 – 2.8U/l. What is the most effective means in treatment from the given below?
A Antibacterial medication
B Glucocorticoids, cytostatics
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 Relapse of viral hepatitis
B Meningitis
C Hepatic encephlopathy
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 Acute viral hepatitis
B Calculous cholecystitis
C Gilbert's disease
D Chronic 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 Essentiale-forte
B Acyclovir
C Remantadinum
D Arabinoside monophosphate
E α-interferon
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 Hepatocirrhosis
B Constrictive pericarditis
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, progressingjaundice. What study may give reasons for such aggravation?
A Determination of alpha-phetoprotein
B Determination of cholesterol ethers
C Determination of serum ammonia
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 Acute viral hepatitis B
B Primary liver cancer
C Chronic viral hepatitis B
D Primary biliary liver cirrhosis
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 Thrombosis of mesenteric vessels
B Hemorrhage from varicosely dilatated veins of esophagus
C Portal hypertension
D Acute stomach ulcer
E Hepatocellular insufficiency
Standard answers: 1-A, 2-B, 3-C, 4-D, 5-E, 6-A, 7-B, 8-C, 9-D, 10-E.
IV. Summarizing, announcing the final grade, announcing the task for the next lesson.
Recommended resources:
- Basic literature source:
1. Norah A. Terrault, Anna S.F. Lok, Brian J. McMahon. Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance // Hepatology.- 2018.- Vol. 67, No. 4. - P. 1560-1599.
2. American Association for the Study of Liver Diseases; Infectious Diseases Society of America. HCV guidance: recommendations for testing, managing, and treating hepatitis C. May 2018.
https://www.hcvguidelines.org/
3. Jacobson IM, Lim JK, Fried MW. American Gastroenterological Association Institute clinical practice update - expert review: care of patients who have achieved a sustained virologic response after antiviral therapy for chronic hepatitis C infection. Gastroenterology. 2017 May;152(6):1578-87.
https://www.gastrojournal.org/article/S0016-5085(17)30327-X/fulltext
4. Singal AK, Bataller R, Ahn J, et al. ACG clinical guideline: alcoholic liver disease. Am J Gastroenterol. 2018 Feb;113(2):175-94.
- Additional literature source:
1. Platt L, Minozzi S, Reed J, et al. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. Cochrane Database Syst Rev. 2017 Sep 18;(9):CD012021.
2. Li Y, Zhou J. Roles of silent information regulator 1-serine/arginine-rich splicing factor 10-lipin 1 axis in the pathogenesis of alcohol fatty liver disease. Exp Biol Med (Maywood). 2017 Jun;242(11):1117-25.

Appendix 1

Example of the primary examination of the patient

Passport data: name and surname, age

Complaints:

nagging pain in the right upper quadrant after drinking alcohol, icterios sclera, yellowness of the skin. In addition, disturbed by constant nausea, burping air, weakness, lack of appetite.

Anamnesis morbi

has a significant medical history of chronic heavy alcohol consumption of about one bottle of wine each day for about 5 years until 1 year ago; since then he has had severe intermittent binge alcohol intake.

Anamnesis vitae

Living conditions are satisfactory. Botkin's disease, tuberculosis, sexually transmitted diseases, malaria denies.

Professional anamnesis: not burdened.

Hereditary history is not burdened.

Pave not been in contact with infectious patients for the last 3 days. He has not left the country in the last 3 years.

***Hereditary history**: not burdened*

Neurological history

At the time of examination signs of focal neurological symptoms were not detected.

***Allergic history**: not burdened*

Epidemiology

Tuberculosis, malaria, viral hepatitis, Botkin's disease, veneral disease, HIV, AIDS, pediculosis – denies.

***Oncoanamnesis**: denies.*

***Insurance anamnesis**: There is no need to issue a seak leave, for the last 12 months a seak leave document has not been issued in this regard.*

***Postponed operations**: denies.*

***Bad habits**: abuses alcohol for 5 years.*

Examination of organ systems:

GENERAL Condition: satisfactory

CONSCIOUSNESS: clear

Body shape: hypostenic

Fatness: low nutrition

POSITION OF THE PATIENT: active

BODY TEMPERATURE: 36.6 C. Signs of alcohol intoxication – yes.

SKIN: Skin of yellowish color, clean. Tissue turgor is normal. Skin pigmentation: depigmentation - no. Rash: no; other changes in the skin: no.

Visible mucous membranes: icterios sclera

LYMPH NODES: not enlarged

THYROID GLAND: no pathology

Oncological examination was performed, no visual forms of oncopathology were detected

Cardiovascular system:

PERCUSSION OF THE HEART: the limits of relative cardiac dullness: right on the right edge of the sternum, upper -III rib on the left parasternalis line, left - 1 cm outward from the left mediaclavicularis line in the V intercostal space

HEART activity: rhythmic, heart rate - 74 per 1 min. Pulse 74 in 1 min. Heart tones: muffled

HEART MURMURS: no

EDEMA: no

BP 125 / 85 mm Hg

EXAMINATION OF ARTERIES: no pathology

VEIN STUDY: no pathology

RESPIRATORY SYSTEM:
BREATHING: no dyspnea at rest, RR 16 in 1 min.
Sputum: no
CHEST: cylindrical, not deformed. Intercostal spaces: NOT smoothed. Participation of additional muscles: no, RR – 16 in 1 min. SpO2 = 98%
Percussion over the lungs: clear lung sound.
PULMONARY AUSCULTATION: vesicular breathing over both lungs. Pleural friction noise - no
DIGESTIVE SYSTEM:
TONGUE: wet; covered with yelowish plaque.
Tonsils: not enlarged
STOMACH: participates in the act of breathing. No hernia. Pulsation in the epigastrium - no. There is no dilation of the subcutaneous veins
Palpation: liver + 2 cm below right costal arch, there is a moderate pain at palpation of liver edge
Pathological symptoms: not detected
Liver: not enlarged
Gallbladder: not palpable
Pancreas: painless
Spleen: not palpable,
PERCUTIONAL SOUND OVER THE ABDOMINAL CAVITY: unchanged,
FECES: normal, no pathological impurities
URINARY SYSTEM:
Palpation of the kidneys: not palpable
Pasternatsky's symptom is negative on both sides.
Urination: free, painless, frequency per day: 3-4 times.
Urinary incontinence: no.
SENSES:
SIGHT: not violated (OU). There is no other pathology
HEARING: normal, no deafness, pain: no. Tinnitus: no.
Musculoskeletal system:
Pathology of the musculoskeletal system was not detected
On the basis of complaints, anamnesis, objective examination, it is possible to make a preliminary diagnosis:
Chronic toxic (alcoholic) hepatitis.
Plan of investigation
general blood test, general urine test, glycemia level (8.00, 13.00, 17.00, 21.00).
Biochemistry: liver tests - total bilirubin and fractions, ALT, AST, glucose, protein, lipid spectrum, coagulogram, amylase, AF, LDH, GGT, CPK, serum iron, CRP, electrolytes (potassium, sodium, calcium, chloride), markers of viral hepatitis, feces test.
ECG, ultrasound of abdomen, ultrasound of the gallbladder with a test breakfast, duodenal probe, FGDS, cholecystography,
Consultation of gastroenterologist.
Treatment plan
Diet.
Refuse to consume alcohol.
Drug therapy:
- Reosorbilact 200 ml intravenouslyfor 10 days
- Heptral 10 ml per 500 ml of 10% glucose solution intravenously for 10 days
- Vitamins B1, B6, B12, folic acid, vitamin PP parenterally for 10 days, then multivitamin complexes for a month
- Essentiale forte - 2 caps. x3 times a day for 3 months

Appendix 2

Tests of basic knowledge level in KROK format

Theme 24. Chronic hepatitis

1. Patient B., 38 years, has been abusing alcohol for half a year. During palpation a moderate liver enlargement is detected, spleen is not enlarged. No free fluid in the abdominal cavity. During a biochemical analysis of blood there is: ALT, AST, bilirubin, blood triglycerides — normal; insignificant increase of γ-glutamiltranspeptidase. During sonography — moderate enlargement of liver, structure is homogeneous, increased echogenicity. Your diagnosis?
A. Chronic alcoholic hepatitis with minimal activity.
B. Fatty hepatosis of alcohol etiology.
C. Alcocholic liver cirrhosis.
D. Nonspecific reactive hepatitis.
E. Liver amyloidosis.
2. Patient's illness was diagnosed as a chronic hepatitis with manifestations of cholestasis with a mild activity. Which of the prescriptions is indicated for the patient?
A. Choleretics.
B. Glucocorticoids.
C. Vitamins.
D. Ursodeoxycholic acid.
E. Hepatoprotectors based on phospholipids.
3. Patient G. is suspected of having transition of a chronic hepatitis into hepatic cirrhosis. This suspicion could be based on:
A. Detection of positive markers of hepatitis C virus.
B. Detection of bilirubinemia.
C. Detection of hypercholesterolemia.
D. Detection of diffuse changes of the liver at sonography.
E. Detection of esophageal varicose veins dilatation.
4. Patient C. has a chronic hepatitis. What pain characteristic is more typical of this disease?
A. Cramping pains in the right part of abdomen.
B. Stinging pains in the right hypochondrium.
C. Compressing pains in epigastric region and right hypochondrium.
D. Nagging pains, heaviness in the right hypochondrium.
E. Burning sensation in the upper part of abdomen.
5. Patient R. has alcoholic cirrhosis of the liver with significant portal hypertension. Choose the medicine for treatment of a portal hypertension.
A. Verospiron.
B. Sulfanilamide.
C. Medicines of a nitrofuran range.
D. Glucocorticosteroids.
E. Hepatoprotectors.
6. Patient suffering from a chronic viral C hepatitis, complains of a significant cutaneous itching. What's the pathogenesis of this complaint?
A. Allergy.
B. Neurasthenia.
C. Cholestasis.
D. Intoxication.
E. Portal systemic encephalopathy.
7. Patient K. complains of heaviness, dull nagging pains in the right hypochondrium, increasing after physical exertion, having no clear connection with taking of food. No attacks of intensive

pains in abdomen. General weakness, cutaneous itching, periodical icteritiousness of skin. What disease is the most probable?
A. Chronic acalculous cholecystitis.
B. Chronic pancreatitis.
C. Chronic hepatitis.
D. Hemolytic anemia.
E. Chronic calculous cholecystitis.
8. 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 mcmol/L, AST- 2,1 mmol/L, ALT- 1,8 mmol/L, alkaline phosphatase - 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
9. 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 mkmol/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
10. A 40-year-old man is ill with autoimmune hepatitis. Blood test: IgA/G ratio 0,8, bilirubin - mcmol/l, transaminase : ALT- 73 U/l, AST – 52 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

Practical lesson #25

1. Theme: Cirrhosis of liver

2. Goal:

To study:

- cirrhosis of liver: definition;
- etiology, pathogenesis of cirrhosis of liver;
- cirrhosis of liver: classification;
- clinic manifestations of cirrhosis of liver;
- diagnosis and differential diagnosis;
- treatment strategies for cirrhosis of liver;
- complications of cirrhosis of liver.

3. Basic concepts. Cirrhosis of liver: definition, aetiology, pathogenesis. Classification. Diagnostics and differential diagnostics. Treatment. Complications. Prognosis.

Cirrhosis is a late stage of hepatic fibrosis that has resulted in widespread distortion of normal hepatic architecture. Cirrhosis is characterized by regenerative nodules surrounded by dense fibrotic tissue. Symptoms may not develop for years and are often nonspecific (eg, anorexia, fatigue, weight loss). Late manifestations include portal hypertension, ascites, and, when decompensation occurs, liver failure. Diagnosis often requires liver biopsy. Cirrhosis is usually considered irreversible. Treatment is supportive.

Cirrhosis is a leading cause of death worldwide. The causes of cirrhosis are the same as those of fibrosis. In developed countries, most cases result from chronic alcohol abuse or chronic hepatitis C. In parts of Asia and Africa, cirrhosis often results from chronic hepatitis B. Cirrhosis of unknown etiology (cryptogenic cirrhosis) is becoming less common as many specific causes (eg, chronic hepatitis C, steatohepatitis) are identified. Injury to the bile ducts also can result in cirrhosis, as occurs in mechanical bile duct obstruction, primary biliary cirrhosis and primary sclerosing cholangitis.

Pathophysiology

There are 2 primary ingredients:

- ✓ Hepatic fibrosis
- ✓ Regenerating liver cells

In response to injury and loss, growth regulators induce hepatocellular hyperplasia (producing regenerating nodules) and arterial growth (angiogenesis). Among the growth regulators are cytokines and hepatic growth factors (eg, epithelial growth factor, hepatocyte growth factor, transforming growth factor-α, tumor necrosis factor). Insulin, glucagon, and patterns of intrahepatic blood flow determine how and where nodules develop.

Angiogenesis produces new vessels within the fibrous sheath that surrounds nodules. These vessels connect the hepatic artery and portal vein to hepatic venules, restoring the intrahepatic circulatory pathways. Such interconnecting vessels provide relatively low-volume, high-pressure venous drainage that cannot accommodate as much blood volume as normal. As a result, portal vein pressure increases. Such distortions in blood flow contribute to portal hypertension, which increases because the regenerating nodules compress hepatic venules.

The progression rate from fibrosis to cirrhosis and the morphology of cirrhosis vary from person to person. Presumably, the reason for such variation is the extent of exposure to the injurious stimulus and the individual's response.

Complications:

Portal hypertension is the most common serious complication of cirrhosis, and it, in turn, causes complications, including GI bleeding from esophageal, gastric, or rectal varices and portal hypertensive gastropathy. In patients with cirrhosis, portal hypertension can also lead to ascites, acute kidney injury (hepatorenal syndrome), and pulmonary hypertension (portopulmonary hypertension). Ascites is a risk factor for spontaneous bacterial peritonitis. Portopulmonary hypertension can manifest with symptoms of heart failure. Complications of portal hypertension tend to cause significant morbidity and mortality.

Cirrhosis can cause other cardiovascular complications. Vasodilation, intrapulmonary right-to-left shunting, and ventilation/perfusion mismatch can result in hypoxia (hepatopulmonary syndrome).

Progressive loss of hepatic architecture impairs function, leading to hepatic insufficiency; it manifests as coagulopathy, acute kidney injury (hepatorenal syndrome), and hepatic encephalopathy. Hepatocytes secrete less bile, contributing to cholestasis and jaundice. Less bile in the intestine causes malabsorption of dietary fat (triglycerides) and fat-soluble vitamins. Malabsorption of vitamin D may contribute to osteoporosis. Undernutrition is common. It may result from anorexia with reduced food intake or, in patients with alcoholic liver disease, from malabsorption due to pancreatic insufficiency.

Blood disorders are common. Anemia usually results from hypersplenism, chronic GI bleeding, folate deficiency (particularly in patients with alcoholism), and hemolysis.

Cirrhosis results in decreased production of prothrombotic and antithrombotic factors. Hypersplenism and altered expression of thrombopoietin contribute to thrombocytopenia. Thrombocytopenia and decreased production of clotting factors can make clotting unpredictable, increasing risk of both bleeding and thromboembolic disease (even though INR is usually increased). Leukopenia is also common; it is mediated by hypersplenism and altered expression of erythropoietin and granulocyte-stimulating factors.

Hepatocellular carcinoma frequently complicates cirrhosis, particularly cirrhosis resulting from chronic hepatitis B or C, hemochromatosis, alcohol-related liver disease, α_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

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)
- ✓ 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:

Imaging tests are not highly sensitive or specific for the diagnosis of cirrhosis by themselves, but they can often detect its complications. 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
- α_1-Antitrypsin deficiency: Confirmed by a low serum α_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.

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, nonalcoholic steatohepatitis (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.

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
PT (seconds prolonged)	< 4	1
	4–6	2
	> 6	3
or		
INR	< 1.7	1
	1.7–2.3	2
	> 2.3	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

*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

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 Na has been extensively studied but is not yet widely used clinically in the US.

For patients ≥ 12 yr, the MELD score is calculated using the following formula:

$$3.8\left[Ln\ serum\ bilirubin\ (mg/dL)\right] + 11.2\left[Ln\ INR\right] + 9.6\left[Ln\ serum\ creatinine\ (mg/dL)\right] + 6.4$$

Ln equals natural logarithm. If a patient has had ≥ 2 hemodialysis treatments or 24 h of continuous venovenous hemodialysis in the week before MELD scoring, creatinine is calculated using 4 mg/dL, the maximum creatinine level allowed in the model. 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.

A MELD score calculator is available at the website of the Organ Procurement and Transplantation Network (OPTN) of the Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services (MELD score calculator).

For patients < 12 yr, the corresponding Pediatric End-Stage Liver Disease (PELD) score is calculated using the following formula:

$$10 \times [0.480 \times Ln\ serum\ bilirubin\ (mg/dL) + 1.857 \times Ln\ INR - 0.687 \times Ln\ serum\ albumin\ (g/dL) + listing\ age\ factor + growth]$$

Ln equals natural logarithm; listing age factor is 0.436 if patients are < 1 yr of age or if they were < 1 yr when added to the transplant list until they are age 2 yr. Growth equals 0.667 if height or weight is > 2 standard deviations below mean values for age. If patients have certain disorders, including urea cycle disorders, organic acidemia, or hepatoblastoma, the PELD score is 30.

Higher PELD scores predict higher risk.

A PELD score calculator is available at the website of the Organ Procurement and Transplantation Network (OPTN) of the Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services (PELD calculator).

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 (see Prognosis). No evidence supports treating small esophageal varices. Medium and large esophageal varices should be treated prophylactically with nonselective β-blockers or endoscopic banding (ligation). If gastric varices are not amenable to endoscopic banding and do not respond to nonselective β-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 α_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.

Primary biliary cirrhosis (PBC)

is an autoimmune liver disorder characterized by the progressive destruction of intrahepatic bile ducts, leading to cholestasis, cirrhosis, and liver failure. Patients usually are asymptomatic at presentation but may experience fatigue or have symptoms of cholestasis (eg, pruritus, steatorrhea) or cirrhosis (eg, portal hypertension, ascites). Laboratory tests reveal cholestasis, increased IgM, and, characteristically, antimitochondrial antibodies in the serum. Liver biopsy may be necessary for diagnosis and staging. Treatment includes ursodeoxycholic acid, cholestyramine (for pruritus), supplementary fat-soluble vitamins, and, ultimately for advanced disease, liver transplantation.

Etiology

PBC is the most common liver disease associated with chronic cholestasis in adults. Most (95%) cases occur in women aged 35 to 70. PBC also clusters in families. A genetic predisposition, perhaps involving the X chromosome, probably contributes. There may be an inherited abnormality of immune regulation. An autoimmune mechanism has been implicated; antibodies to antigens located on the inner mitochondrial membranes occur in > 95% of cases. These antimitochondrial antibodies (AMAs), the serologic hallmarks of PBC, are not cytotoxic and are not involved in bile duct damage. PBC is associated with other autoimmune disorders, such as RA, systemic sclerosis, Sjögren syndrome, CREST syndrome, autoimmune thyroiditis, and renal tubular acidosis.

T cells attack the small bile ducts. CD4 and CD8 T lymphocytes directly target biliary epithelial cells. The trigger for the immunologic attack on bile ducts is unknown. Exposure to foreign antigens, such as an infectious (bacterial or viral) or toxic agent, may be the instigating event. These foreign antigens might be structurally similar to endogenous proteins (molecular mimicry); then the subsequent immunologic reaction would be autoimmune and self-perpetuating. Destruction and loss of bile ducts lead to impaired bile formation and secretion (cholestasis). Retained toxic materials such as bile acids then cause further damage, particularly to hepatocytes. Chronic cholestasis thus leads to liver cell inflammation and scarring in the periportal areas. Eventually, hepatic inflammation decreases as hepatic fibrosis progresses to cirrhosis.

Autoimmune cholangitis is sometimes considered to be a separate disorder. It is characterized by autoantibodies, such as antinuclear antibodies (ANAs), anti–smooth muscle antibodies, or both and has a clinical course and response to treatment that are similar to PBC. However, in autoimmune cholangitis, AMAs are absent.

Symptoms and Signs

About half of patients present without symptoms. Symptoms or signs may develop during any stage of the disease and may include fatigue or reflect cholestasis (and the resulting fat malabsorption, which may lead to vitamin deficiencies and osteoporosis), hepatocellular dysfunction, or cirrhosis.

Symptoms usually develop insidiously. Pruritus, fatigue, and dry mouth and eyes are the initial symptoms in > 50% of patients and can precede other symptoms by months or years. Other initial manifestations include right upper quadrant discomfort (10%); an enlarged, firm, nontender liver (25%); splenomegaly (15%); hyperpigmentation (25%); xanthelasmas (10%); and jaundice (10%). Eventually, all the features and complications of cirrhosis occur. Peripheral neuropathy and other autoimmune disorders associated with PBC may also develop.

Diagnosis

- ✓ Liver function tests
- ✓ Antimitochondrial antibodies
- ✓ Ultrasonography and often MRCP
- ✓ Liver biopsy

In asymptomatic patients, PBC is detected incidentally when liver function tests detect abnormalities, typically elevated levels of alkaline phosphatase and γ-glutamyl transpeptidase (GGT). PBC is suspected in middle-aged women with classic symptoms (eg, unexplained pruritus, fatigue, right upper quadrant discomfort, jaundice) or laboratory results suggesting cholestatic liver disease: elevated alkaline phosphatase and GGT but minimally abnormal aminotransferases (ALT, AST). Serum bilirubin is usually normal in the early stages; elevation indicates disease progression and a worsening prognosis.

If PBC is suspected, liver function tests and tests to measure serum IgM (increased in PBC) and AMA should be done. Enzyme-linked immunosorbent assay (ELISA) tests are 95% sensitive and 98% specific for PBC; false-positive results can occur in autoimmune hepatitis (type 1). Other autoantibodies (eg, ANAs, anti–smooth muscle antibodies, rheumatoid factor) may be present. Extrahepatic biliary obstruction should be ruled out. Ultrasonography is often done first, but ultimately MRCP and sometimes ERCP are necessary. Unless life expectancy is short or there is a contraindication, liver biopsy is usually done. Liver biopsy confirms the diagnosis; it may detect pathognomonic bile duct lesions, even in early stages. As PBC progresses, it becomes morphologically indistinguishable from other forms of cirrhosis. Liver biopsy also helps stage PBC, which has 4 histologic stages:

- ✓ Stage 1: Inflammation, abnormal connective tissue, or both, confined to the portal areas
- ✓ Stage 2: Inflammation, fibrosis, or both, confined to the portal and periportal areas
- ✓ Stage 3: Bridging fibrosis
- ✓ Stage 4: Cirrhosis

Autoimmune cholangitis is diagnosed when AMAs are absent in a patient who otherwise would be diagnosed with PBC.

Prognosis

Usually, PBC progresses to terminal stages over 15 to 20 yr, although the rate of progression varies. PBC may not diminish quality of life for many years. Patients who present without symptoms tend to develop symptoms over 2 to 7 yr but may not do so for 10 to 15 yr. Once symptoms develop, median life expectancy is 10 yr. Predictors of rapid progression include the following:

- ✓ Rapid worsening of symptoms
- ✓ Advanced histologic changes
- ✓ Older patient age
- ✓ Presence of edema
- ✓ Presence of associated autoimmune disorders
- ✓ Abnormalities in bilirubin, albumin, PT, or INR

The prognosis is ominous when pruritus disappears, xanthomas shrink, jaundice develops, and serum cholesterol decreases.

Treatment

- ✓ Arresting or reversing liver damage
- ✓ Treating complications (chronic cholestasis and liver failure)
- ✓ Sometimes liver transplantation

All alcohol use and hepatotoxic drugs should be stopped. Ursodeoxycholic acid (15 mg/kg po once/day) decreases liver damage, prolongs survival, and delays the need for liver transplantation. About 20% of patients do not have biochemical improvement after ≥ 4 mo; they may have advanced disease and require liver transplantation in a few years. Other drugs proposed to decrease liver damage have not improved overall clinical outcomes or are controversial.

Pruritus may be controlled with cholestyramine6 to 8 g po bid. This anionic-binding drug binds bile salts and thus may aggravate fat malabsorption. If cholestyramine is taken long-term, supplements of fat-soluble vitamins should be considered. Cholestyraminecan decrease absorption of ursodeoxycholic acid, so these drugs should not be given simultaneously. Cholestyramine can also decrease absorption of various drugs; if patients take any drug that could be affected, they should be told not to take the drug within 3 h before or after taking cholestyramin.

Some patients with pruritus respond to ursodeoxycholic acid and ultraviolet light; others may warrant a trial of rifampin or an opioid antagonist, such as naltrexone.

Patients with fat malabsorption due to bile salt deficiency should be treated with vitamin A, D, E, and K supplements. For osteoporosis, weight-bearing exercises, bisphosphonates, or raloxifene may be needed in addition to Ca and vitamin D supplements. In later stages, portal hypertension or complications of cirrhosis require treatment.

Liver transplantation has excellent results. The general indication is decompensated liver disease (uncontrolled variceal bleeding, refractory ascites, intractable pruritus, and hepatic encephalopathy). Survival rates after liver transplantation are > 90% at 1 yr, > 80% at 5 yr, and > 65% at 10 yr. AMAs tend to persist after transplantation. PBC recurs in 15% of patients in the first few years and in > 30% by 10 yr. Recurrent PBC after liver transplantation appears to have a benign course. Cirrhosis rarely occurs.

Key Points

- ✓ PBC is a chronic, progressive cholestatic liver disorder that is caused by an autoimmune attack on small bile ducts and that occurs almost exclusively in women aged 35 to 70.
- ✓ PBC typically progresses to a terminal stage over 15 to 20 yr.
- ✓ Suspect PBC if patients have unexplained elevated alkaline phosphatase and GGT but minimally abnormal aminotransferases, particularly if they have constitutional symptoms or manifestations of cholestasis (eg, pruritis, osteoporosis, vitamin D deficiency).
- ✓ Measure IgM and anti-mitochondrial antibodies, and do imaging (to rule out extrahepatic biliary obstruction) and liver biopsy.
- ✓ Stop use of hepatotoxins (including alcohol), and treat with ursodeoxycholic acid, which may delay the need for transplantation.
- ✓ Transplantation is indicated for decompensated liver disease (uncontrolled variceal bleeding, refractory ascites, intractable pruritus, hepatic encephalopathy).

4. **Equipment:** study room, ultrasound system “Mylab Six CristaLine”. Students acknowledge with protocol and procedure of liver and biliary tract investigation, visit functional department (1st floor in University Clinic). Results of these investigations are provided to applicants during lesson.
5. **Learning hours:** 4 hours.

Plan of the lesson

I. Organizational moment (greetings, checking who is present on the lesson, announcing topic and goal of the lesson, motivating applicants to study the topic).

II. Control of basic knowledge (oral questioning, tests, checking of how clinical cases and workbooks are fulfilled).

2.1. Demands for applicants theoretical preparation

Didactic units list:

1. Cirrhosis of liver: definition.
2. Etiology, pathogenesis.
3. Classification.

4. Clinical features.
5. Criteria of diagnostics.
6. Differential diagnosis.
7. Complications of cirrhosis of liver.
8. Treatment approaches and strategies.
9. Prognosis for life, convalescence and work capacity.

Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Tests for self-control

1. Patient with hepatic cirrhosis has lethargy, weakness, nausea, disturbance of sleep at night time and sleepiness at day, sweetish smell from mouth. Manifestation of what syndrome is this?
A. Cholestatic.
B. Hyperazotemia. +
C. Cytolytic.
D. Portal hypertension.
E. Hypersplenism.

2. Patient suffering from a chronic hepatitis had a regular examination where change of liver palpatory properties was detected: it has become denser, than 5-6 months ago, edge became sharp, but size of liver hasn't changed. What can the change of results of liver palpation be evidence of?
A. Development of portal hypertension.
B. Increasing of necrosis of hepatocytes.
C. Joining of cholestasis.
D. Transformation of chronic hepatitis into hepatic cirrhosis. +
E. Hepatotoxic influence of medicines.

3. 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 mcmol/L, AST- 2,1 mmol/L, ALT- 1,8 mmol/L, alkaline phosphatase - 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

4. 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, spleen 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

5.Patient with liver cirrhosis has the following in blood: erythrocytes — 2,8 T/L, leukocytes — 3,3 G/L, thrombocytes — 100000 in 1ml of blood. Of which syndrome is it typical?
A. Cytolytic.
B. Cholestatic.
C. Hyperazotemia.
D. Hypersplenism.+
E. Portal hypertension.

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 jaundice 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. Patient's illness was diagnosed as cirrhosis of liver with manifestations of cholestasis with a mild activity. Which of the prescriptions is indicated for the patient?
A. Choleretics.
B. Glucocorticoids.
C. Vitamins.
D. Ursodeoxycholic acid. +
E. Hepatoprotectors based on phospholipids.
8. Patient G. is suspected of having transition of a chronic hepatitis into hepatic cirrhosis. This suspicion could be based on:
A. Detection of positive markers of hepatitis C virus.
B. Detection of bilirubinemia.
C. Detection of hypercholesterolemia.
D. Detection of diffuse changes of the liver at sonography.+
E. Detection of esophageal varicose veins dilatation.
9. Patient P., 60 years old, suffers from hepatic cirrhosis in the outcome of a viral C hepatitis. The detection of the disease stage according to Child-Pugh was done to reveal indications for the liver transplantation. Sum of points — 9. What stage of hepatic cirrhosis does the patient have?
A. Stage A-I.
B. Stage A-II.
C. Stage A-III.
D. Stage B. +
E. Stage C.
10.Patient R. has alcoholic cirrhosis of the liver with significant portal hypertension. Choose the medicine for treatment of a portal hypertension.
A. Verospiron. +
B. Sulfanilamide.
C. Medicines of a nitrofuran range.
D. Glucocorticosteroids.
E. Hepatoprotectors
III. Formation of professional skills, abilities:
3.1. content of tasks (tasks, clinical situations, etc.)
Case history #1
A 56-year-old man with a remote history of intravenous drug use presents to an initial visit complaining of increased abdominal girth but denies jaundice. He drinks about 2 to 4 glasses of wine with dinner and recalls having had abnormal liver enzymes in the past. Physical examination reveals spider naevi, a palpable firm liver, mild splenomegaly, and shifting dullness consistent with the presence of ascites. Liver function is found to be deranged with elevated aminotransferases (aspartate aminotransferase [AST]: 90 U/L, alanine aminotransferase [ALT]: 87 U/L), and the patient is positive for anti-hepatitis C antibody.
Case history #2
A 60-year-old woman with a past medical history of obesity, diabetes, and dyslipidaemia is noted to have abnormal liver enzymes with elevated aminotransferases (ALT: 68 U/L, AST: 82 U/L), and normal alkaline phosphatase and bilirubin. She denies significant alcohol consumption, and tests for viral hepatitis and autoimmune markers are negative. An abdominal ultrasound reveals evidence of fatty infiltration of the liver and slight enlargement of the spleen.

Task: Applicant should write diagnosis, plan of investigation, carry out differential diagnosis, prescribe treatment for these case histories.

3.2. recommendations (instructions) for performing tasks (professional algorithms, orientation maps for the formation of practical skills, etc.)

Professional algorithms.

XXII. Patient's examination.

During patient's examination students should keep such communicative skills:

1. Friendly face expression.
2. Kind voice tone.
3. Greetings, showing concern and respect about the patient.
4. Find out patient's complaints and anamnesis .
5. Explanation of specific actions (hospitalization, carrying out investigations) which are planned to be performed in the future.
6. Student should perform liver palpation and percussion.
7. Finishing of the talk.

XXIII. Patient's investigation algorithm.

1. It should be explained to patient which investigation will be held and indications for this investigation.
2. A doctor should receive patient's agreement on investigation.
3. A doctor should warn patient about possibilities of unpleasant feelings during investigation.
4. Results of investigation should be explained to a patient.
5. Liver function test should be done: check of ALT, AST, AP, GGT, Bilirubin, Total protein, Albumin values.
6. Serum HBeAg, HBV DNA, serum anti-HBe, HBV and HCV genotype, anti-HCV antibodies, HCV RNA should be checked.
7. Urea, electrolytes, serum sodium, ammonia level and folate should be checked.
8. Iron studies (for haemochromatosis) and copper studies plus serum ceruloplasmin (for Wilson's disease) should be done.
9. Coagulation profile should be determined. Platelet count should be measured.
10. Gamma-globulin levels should be checked.
11. Anti-nuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) should be checked.
12. Anti-soluble liver antigens or liver/pancreas (anti-SLA/LP) are highly specific markers of autoimmune hepatitis, which led to cirrhosis.
13. Antibodies to liver/kidney microsome type 1 antigen (anti-LKM-1 antibodies) are characteristic serological marker for the diagnosis of type 2 type of autoimmune hepatitis, which led to cirrhosis.
14. Cytokeratin-18 fragments - biomarkers may be able to detect the degree of liver injury without the need for liver biopsy.
15. Plasma alpha-1 antitrypsin should be checked.
16. Liver ultrasound should be done: signs of portal hypertension: ascites, splenomegaly, increased diameter of the portal vein (≥13 mm), or collateral vessels will be revealed. In combination with a strong clinical suspicion, the above findings suffice for the diagnosis of cirrhosis without the need of a confirmatory liver biopsy.
17. Liver biopsy is used to assess the degree of liver damage and to rule out causes of liver disease. Architectural distortion of the liver parenchyma with formation of regenerative nodules will be detected.
18. On abdominal CT signs of advanced cirrhosis may be detected using abdominal crossectional imaging. Signs of portal hypertension: ascites, splenomegaly, collateral circulation.
19. Patients with cirrhosis should be offered upper gastrointestinal endoscopy for screening of gastrooesophageal varices at the time of diagnosis.

20. Alpha Fetoprotein level is used for screening for hepatocellular carcinoma in conjunction with ultrasound every 6 to 12 months in high-risk HBV carriers.
21. Ultrasound-based elastography is a useful tool for detecting hepatic fibrosis and cirrhosis without the need for liver biopsy.
22. Every patient with new-onset ascites should undergo a diagnostic paracentesis: cell count with differential, albumin, and total protein should be measured in the ascitic fluid. Ascitic fluid should also be sent for cytology.

XXIV. Step-by-step algorithm of treatment.

1. A patient should informed be about necessity of the prescribed treatment.
2. Dosages, drugs intake regimens, duration of treatment, side effects of the prescribed therapy should be kindly explained to patient.
3. As cirrhosis is the pathological end-stage of any chronic liver disease, it is essential to treat the underlying causative condition such as hepatitis B and C virus infections, alcohol-related liver disease, haemochromatosis, Wilson's disease, alpha-1 antitrypsin deficiency, glycogen storage diseases, abetalipoproteinaemia, primary biliary cholangitis, primary sclerosing cholangitis, autoimmune hepatitis, biliary atresia, cystic fibrosis, or Budd-Chiari syndrome in order to slow or halt the progression of cirrhosis.
4. American Association for the Study of Liver Diseases recommendations for treatment regimens in HCV:

- Daclatasvir plus sofosbuvir
- Elbasvir/grazoprevir
- Glecaprevir/pibrentasvir
- Ledipasvir/sofosbuvir
- Ombitasvir/paritaprevir/ritonavir ± dasabuvir
- Sofosbuvir plus simeprevir
- Sofosbuvir/velpatasvir
- Sofosbuvir/velpatasvir/voxilaprevir.

5. There are several agents currently approved for the treatment of chronic HBV: interferon alfa 2b, peginterferon alfa 2a, and the nucleoside/nucleotide analogues. The nucleoside analogues are entecavir and lamivudine. The nucleotide analogues are tenofovir disoproxil and adefovir. The preferred first-line single drug choices are entecavir, peginterferon alfa-2a, and tenofovir disoproxil.
6. In fatty liver hepatitis Orlistat can be used. It is an enteric lipase inhibitor that prevents the absorption of fats from the gastrointestinal tract.
7. Systematic reviews have found that thiazolidinediones (pioglitazone, rosiglitazone) improve liver histological scores in patients with non-alcoholic fatty liver disease (NAFLD).
8. Atorvastatin and antioxidants (vitamins C and E) reduce the odds of hepatic steatosis in patients with hepatic steatosis.
9. In patients with autoimmune hepatitis regimen of prednisone/prednisolone plus azathioprine as an initial treatment option.
10. Mycophenolate and ciclosporin may be considered as alternative immunosuppressants to azathioprine for patients who are intolerant to azathioprine in patients with autoimmune hepatitis.
11. To manage ascitis in liver cirrhosis first-line choice of diuretic should be spironolactone due to its effects on aldosterone. Furosemide may be added in patients who do not respond.
12. Some patients may develop large volume ascites refractory to medical treatment because of lack of efficacy, or unacceptable adverse effects or complications. These patients may require recurrent large volume paracentesis and albumin replacement for symptom control.
13. Patients not suitable for liver transplantation should be considered for transjugular intrahepatic portosystemic shunt (TIPSS) placement.

14. Prophylaxis with either non-selective beta-blockers (propranolol, nadolol, or carvedilol) or endoscopic variceal ligation (EVL), which requires several sessions to obliterate varices, should be implemented if gastro-oesophageal varices are present.
15. Acute variceal haemorrhage. An episode of acute variceal haemorrhage should be managed as a medical emergency with intravascular volume support, blood transfusion (with the aim of keeping the haemoglobin around 70-80 g/L, and a combination of endoscopic and pharmacological therapy. Terlipressin (a vasopressin analogue), or somatostatin or its analogue octreotide should be initiated as soon as a variceal bleed is suspected and continued for 3-5 days if it is confirmed. Upper gastrointestinal endoscopy should be performed within 12 hours to confirm the diagnosis and allow treatment with sclerotherapy. Short-term (up to 7 days) antibiotic prophylaxis with norfloxacin should be instituted in all patients following a gastrointestinal haemorrhage (regardless of the presence of ascites) as this has been shown to decrease the rate of bacterial infections and increase survival.
16. For treatment of spontaneous bacterial peritonitis intravenous cefotaxime or a fluoroquinolone and intravenous human albumin solution are used.
17. Patients who develop complications of cirrhosis such as hepatocellular carcinoma or signs of decompensation (ascites, jaundice, variceal haemorrhage, portal systemic encephalopathy, hepatopulmonary syndrome or hepatorenal syndrome) should be referred for liver transplant evaluation without delay.

3.3. requirements for applicants work results.

As a results of studying applicants must perform the following:

-possess skills of communication and clinical examination of a patient with cirrhosis of liver;

-collect data on patient complaints, medical history, life history;

-evaluate information about the diagnosis of cirrhosis of liver using a standard procedure, based on the results of laboratory and instrumental studies;

-determine the list of required clinical, laboratory and instrumental studies and evaluate their results;

- identify the leading clinical symptom or syndrome;

- establish the most probable or syndrom diagnosis;

-assign laboratory and instrumental investigations for patient;

-carry out differential diagnosis in different types of cirrhosis of liver;

-establish preliminary and clinical diagnosis;

- determine the principles of treatment, diet regimen for the patient.

3.4. control materials for the final stage of the lesson.

Work 1

1. Collection of complaints, anamnesis, examination of a patients with cirrhosis of liver.
2. Detection of clinical and instrumental symptoms.
3. Grouping symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data.
6. Carrying out a differential diagnosis.
7. Formulation of the clinical diagnosis.
8. Write a prescription list for patients diagnosed with cirrhosis of liver, which would include diet and prescribed drugs.
9. Determining of the disability degree.

Work 2.

Assignment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the department library with thematic literature.

The applicant fills in the protocol of the patient's examination. An example of the initial examination of the patient is attached.

The tests for self-control with standard answers.

1. 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

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

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

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

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

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

6. 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
7. 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 – 2.8U/l. What is the most effective means in treatment from the given below?
A Antibacterial medication
B Glucocorticoids, cytostatics
C Hepatoprotectors
D Antiviral medications
E Hemosorbtion, vitamin therapy
8. 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 Relapse of viral hepatitis
B Meningitis
C Hepatic encephlopathy
D Cholangitis
E Infectious-toxic shock
9. 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 Acute viral hepatitis
B Calculous cholecystitis
C Gilbert's disease
D Chronic viral hepatitis
E Chronic cholangitis
10. 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 Essentiale-forte
B Acyclovir
C Remantadinum
D Arabinoside monophosphate
E α-interferon
Standard answers: 1-A, 2-B, 3-C, 4-D, 5-E, 6-A, 7-B, 8-C, 9-D, 10-E.
IV. Summarizing, announcing the final grade, announcing the task for the next lesson.
Recommended resources:
- Basic literature source:
1. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis / Journal of Hepatology. – 2018.- Vol. 69, issue 2. - P. 406-460
2. D'Amico G, Morabito A, D'Amico M, et al. Clinical states of cirrhosis and competing risks. J Hepatol. 2018 Mar;68(3):563-76.
- Additional literature source:
1. Ortega-Alonso A, Andrade RJ. Chronic liver injury induced by drugs and toxins. J Dig Dis. 2018 Sep;19(9):514-21.

Appendix 1

Example of the primary examination of the patient

Passport data: name and surname, age

Complaints: increased abdominal girth, severe weakness, dizziness, bloating, temperature rise up to 37.3 degrees, nausea.

Anamnesis morbi

has a significant medical history of chronic heavy alcohol consumption of about one bottle of wine each day for about 5 years until 1 year ago; since then he has had severe intermittent binge alcohol intake.

Anamnesis vitae

Living conditions are satisfactory. Botkin's disease, tuberculosis, sexually transmitted diseases, malaria denies.

Professional anamnesis: not burdened.

Hereditary history is not burdened.

Pave not been in contact with infectious patients for the last 3 days. He has not left the country in the last 3 years.

***Hereditary history**: not burdened*

Neurological history

At the time of examination signs of focal neurological symptoms were not detected.

***Allergic history**: not burdened*

Epidemiology

Tuberculosis, malaria, viral hepatitis, Botkin's disease, veneral disease, HIV, AIDS, pediculosis – denies.

***Oncoanamnesis**: denies.*

***Insurance anamnesis**: There is no need to issue a seak leave, for the last 12 months a seak leave document has not been issued in this regard.*

***Postponed operations**: denies.*

***Bad habits**: abuses alcohol for 5 years.*

Examination of organ systems:

GENERAL Condition: satisfactory

CONSCIOUSNESS: apatic

Body shape: hypostenic

Fatness: low nutrition

POSITION OF THE PATIENT: active

BODY TEMPERATURE: 36.6 C. Signs of alcohol intoxication – yes.

SKIN: Skin of yellowish color, clean. Tissue turgor is normal. Skin pigmentation: depigmentation - hyperemia of the face and palms, vascular asterisks on the body. Rash: no; other changes in the skin: no.

Visible mucous membranes: icterios sclera

LYMPH NODES: not enlarged

THYROID GLAND: no pathology

Oncological examination was performed, no visual forms of oncopathology were detected

Cardiovascular system:

PERCUSSION OF THE HEART: the limits of relative cardiac dullness: right on the right edge of the sternum, upper -III rib on the left parasternalis line, left - 1 cm outward from the left mediaclavicularis line in the V intercostal space

HEART activity: rhythmic, heart rate - 74 per 1 min. Pulse 74 in 1 min. Heart tones: muffled

HEART MURMURS: no

EDEMA: no

BP 125 / 85 mm Hg

EXAMINATION OF ARTERIES: no pathology

VEIN STUDY: no pathology

RESPIRATORY SYSTEM:
BREATHING: no dyspnea at rest, RR 16 in 1 min.
Sputum: no
CHEST: cylindrical, not deformed. Intercostal spaces: NOT smoothed. Participation of additional muscles: no, RR – 16 in 1 min. SpO2 = 98%
Percussion over the lungs: clear lung sound.
PULMONARY AUSCULTATION: vesicular breathing over both lungs. Pleural friction noise - no
DIGESTIVE SYSTEM:
TONGUE: wet; covered with yelowish plaque.
Tonsils: not enlarged
STOMACH: participates in the act of breathing, increased in volume due to ascites. No hernia. Pulsation in the epigastrium - no. Dilatation of the subcutaneous veins of the anterior abdominal wall is visualized.
Palpation: slight diffuse pain on palpation of all parts of the abdominal cavity, deep palpation is not available.
Palpation: is not available
Pathological symptoms: not detected
Liver: cannot be palpated
Gallbladder: not palpable
Pancreas: cannot be palpated
Spleen: cannot be palpated
PERCUTIONAL SOUND OVER THE ABDOMINAL CAVITY: shortness of percussion sound
FECES: normal, no pathological impurities
URINARY SYSTEM:
Palpation of the kidneys: not palpable
Pasternatsky's symptom is negative on both sides.
Urination: free, painless, frequency per day: 3-4 times.
Urinary incontinence: no.
SENSES:
SIGHT: not violated (OU). There is no other pathology
HEARING: normal, no deafness, pain: no. Tinnitus: no.
Musculoskeletal system:
Pathology of the musculoskeletal system was not detected
On the basis of complaints, anamnesis, objective examination, it is possible to make a preliminary diagnosis:
Cirrhosis of the liver of alcoholic origin, uncompensated. Hepatocellular insufficiency: jaundice. Portal hypertension: ascites.
Plan of investigation
general blood test, general urine test, glycemia level (8.00, 13.00, 17.00, 21.00).
Biochemistry: liver tests - total bilirubin and fractions, ALT, AST, glucose, protein, lipid spectrum, coagulogram, amylase, AF, LDH, GGT, CPK, serum iron, CRP, electrolytes (potassium, sodium, calcium, chloride), markers of viral hepatitis, feces test.
ECG, ultrasound of abdomen, ultrasound of the gallbladder with a test breakfast, duodenal probe, FGDS, cholecystography,
Consultation of gastroenterologist.
Treatment plan
Diet.
Refuse to consume alcohol.
Drug therapy:
- Heptral 10 ml per 500 ml of 10% glucose solution intravenously for 10 days
- Hofitol 10 ml i.v. for 10 days
- Lipoic acid 4 ml of 0.5% solution intravenously for 10 days

- Vitamins B1, B6, B12, folic acid, vitamin PP parenterally for 10 days, then multivitamin complexes for a month
- Essentiale forte - 2 caps. x3 times a day for 3 months
- Verospirone 0.25 - 2 tab. x2 times a day for 3 weeks
- Trifas 10 mg - 1 tab. in the morning on an empty stomach for 3 weeks
- Ursofalk - 250 mg - 3 tablets at night for 2-3 months

Appendix 2

Tests of basic knowledge level in KROK format

Theme 25. Cirrhosis of liver

1. 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 jaundice 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
2. Patient's illness was diagnosed as cirrhosis of liver with manifestations of cholestasis with a mild activity. Which of the prescriptions is indicated for the patient?
A. Choleretics.
B. Glucocorticoids.
C. Vitamins.
D. Ursodeoxycholic acid.
E. Hepatoprotectors based on phospholipids.
3**.** Patient G. is suspected of having transition of a chronic hepatitis into hepatic cirrhosis. This suspicion could be based on:
A. Detection of positive markers of hepatitis C virus.
B. Detection of bilirubinemia.
C. Detection of hypercholesterolemia.
D. Detection of diffuse changes of the liver at sonography.
E. Detection of esophageal varicose veins dilatation.
4. Patient P., 60 years old, suffers from hepatic cirrhosis in the outcome of a viral C hepatitis. The detection of the disease stage according to Child-Pugh was done to reveal indications for the liver transplantation. Sum of points — 9. What stage of hepatic cirrhosis does the patient have?
A. Stage A-I.
B. Stage A-II.
C. Stage A-III.
D. Stage B.
E. Stage C.
5. Patient R. has alcoholic cirrhosis of the liver with significant portal hypertension. Choose the medicine for treatment of a portal hypertension.
A. Verospiron.
B. Sulfanilamide.
C. Medicines of a nitrofuran range.
D. Glucocorticosteroids.
E. Hepatoprotectors

6. Patient with hepatic cirrhosis has lethargy, weakness, nausea, disturbance of sleep at night time and sleepiness at day, sweetish smell from mouth. Manifestation of what syndrome is this?
A. Cholestatic.
B. Hyperazotemia.
C. Cytolytic.
D. Portal hypertension.
E. Hypersplenism.
7. Patient suffering from a chronic hepatitis had a regular examination where change of liver palpatory properties was detected: it has become denser, than 5-6 months ago, edge became sharp, but size of liver hasn't changed. What can the change of results of liver palpation be evidence of?
A. Development of portal hypertension.
B. Increasing of necrosis of hepatocytes.
C. Joining of cholestasis.
D. Transformation of chronic hepatitis into hepatic cirrhosis.
E. Hepatotoxic influence of medicines.
8. 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 mcmol/L, AST- 2,1 mmol/L, ALT- 1,8 mmol/L, alkaline phosphatase - 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
9. 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, spleen 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
10. Patient with liver cirrhosis has the following in blood: erythrocytes — 2,8 T/L, leukocytes — 3,3 G/L, thrombocytes — 100000 in 1ml of blood. Of which syndrome is it typical?
A. Cytolytic.
B. Cholestatic.
C. Hyperazotemia.
D. Hypersplenism.
E. Portal hypertension.

Practical lesson #26

1. Theme: Chronic pancreatitis

2. Goal:

To study:

- chronic pancreatitis: definition;
- etiology, pathogenesis of chronic pancreatitis;
- chronic pancreatitis: classification;
- clinic manifestations of chronic pancreatitis;
- diagnosis and differential diagnosis;
- treatment strategies for chronic pancreatitis;
- complications of chronic pancreatitis.

3. Basic concepts. Chronic pancreatitis: definition, aetiology, pathogenesis. Classification. Diagnostics and differential diagnostics. Treatment. Complications. Prognosis.

DEFINITION

Pancreatitis is a clinical diagnosis defined by pancreatic inflammation. Although not always clinically distinguishable, pancreatitis can be defined as acute or chronic. Acute pancreatitis is a self-limiting and reversible pancreatic injury associated with mid-epigastric abdominal pain and elevated serum pancreatic enzymes, whereas chronic pancreatitis is characterised by recurrent or persistent abdominal pain and progressive injury to the pancreas and surrounding structures, resulting in scarring and loss of function. In those with recurrent attacks of pancreatitis, identifying the cause and type of pancreatitis involves distinguishing between 4 entities:

1. *Recurrent acute pancreatitis*: there is an identifiable cause of acute pancreatitis that does not lead to chronic pancreatitis (e.g., gallstones, drugs, hypercalcaemia, etc.).
2. *Idiopathic pancreatitis:* exhaustive evaluation identifies no cause. Most commonly this represents chronic relapsing pancreatitis or definite chronic pancreatitis.
3. *Chronic relapsing pancreatitis*: patients have relapsing pain not recognised clinically as chronic pancreatitis (no hallmark features) but have pathological changes.
4. *Established chronic pancreatitis:* hallmark features of chronic pancreatitis are present, including reduced pancreatic exocrine function, malabsorption, diabetes, and pancreatic calcifications.

AETIOLOGY

- the major causes of chronic pancreatitis are alcohol (70% to 80%), followed by idiopathic chronic pancreatitis and other categories. Most patients report alcohol consumption over 150 g per day for years, but the risk of chronic pancreatitis is increased with consumption of only 25 g per day or more (around 2 drinks);
- cigarette smoking;
- high fat/protein diet;
- genetic predisposition (e.g., UDP glucuronosyltransferase gene polymorphisms);
- possibly coxsackievirus infections.

PATHOPHYSIOLOGY

Traditional theories to explain the pathogenesis of chronic pancreatitis include: oxidative stress, toxic-metabolic factors, ductal obstruction, and necrosis-fibrosis.

The primary duct hypothesis suggests that the first insult begins in pancreatic ducts as a primary autoimmune or inflammatory reaction, whereas the sentinel acute pancreatitis event hypothesis suggests that the first insult occurs in acinar cells, triggering sequestration of inflammatory cells and secretion of cytokines.

Removal of the inciting factor(s) results in healing, but with persistent cytokine secretion, fibrogenic pancreatic stellate cells (PSCs) secrete collagen and set the stage for fibrosis and chronic pancreatitis.

The mechanisms of pain in chronic pancreatitis are unclear but are likely to be multi-factorial, including pancreatic inflammation, fibrosis-related increases in intra-pancreatic pressure and ischaemia, neural sources of pain (nerve sheath inflammation, fibrotic encasement of sensory nerves, and neuropathy), and extra-pancreatic causes (e.g., common bile duct stenosis, duodenal stenosis, and pancreatic pseudocysts). A major focus of current investigation is the neuropathic origins of pain.

CLASSIFICATION

Sarles classification

Sarles classified chronic pancreatitis into 3 major groups:

- Obstructive pancreatitis
- Inflammatory pancreatitis
- Lithogenic or calcifying chronic pancreatitis.

TIGAR-O

The TIGAR-O aetiological classification of chronic pancreatitis incorporates insights into genetic, environmental, immunological, and pathobiological risk factors associated with chronic pancreatitis.The TIGAR-O aetiological classification consists of 6 groups:

1. Toxic-metabolic
    - Alcoholic
    - Tobacco smoking
    - Hypercalcaemia
    - Hyperlipidaemia
    - Chronic kidney disease
    - Medicines: phenacetin abuse (weak association)
    - Toxins: organotin compounds, for example, di-N-butyltin dichloride (DBTC)
2. Idiopathic
    - Early onset
    - Late onset
    - Tropical
3. Genetic
    - Hereditary pancreatitis: cationic trypsinogen mutations
    - Cystic fibrosis transmembrane conductance regulator (CFTR) mutations
    - Serine protease inhibitor Kazal type 1 (SPINK1) mutations
    - Chymotrypsinogen C (CTRC) mutations
    - Calcium-sensing receptor (CaSR, CSR) mutations
    - Claudin-2 (CLDN2) mutations
    - Carboxypeptidase A1 (CPA1)
    - Fucosyltransferase 2 (FUT2) non-secretor status
    - ABO blood group type B
4. Autoimmune
    - Isolated autoimmune chronic pancreatitis
    - Syndromic autoimmune chronic pancreatitis associated with Sjogren's syndrome, inflammatory bowel disease, primary biliary cirrhosis
5. Recurrent and severe acute pancreatitis
    - Post-necrotic (severe acute pancreatitis)
    - Recurrent acute pancreatitis
    - Vascular diseases/ischaemia
    - Post-irradiation
6. Obstructive
    - Pancreas divisum (controversial)

- Sphincter of Oddi disorders (controversial)
- Duct obstruction (e.g., solid tumour, intra-ductal papillary mucinous neoplasm)
- Peri-ampullary duodenal wall cysts
- Post-traumatic pancreatic duct scars.

Risk factors

Strong	Weak
Alcohol	high-fat, high-protein diet
Smoking	Tropical geography (for example, tropical pancreatitis is prevalent in specific geographical regions and associated with SPINK1 gene mutations).
Family history	
Coeliac disease	

KEY DIAGNOSTIC FACTORS

- Presence of risk factors (common)
- Abdominal pain (common): pain is epigastric, dull, radiating to the back, diminished by sitting forwards, worse approximately 30 minutes post-prandially. Ammann classifies pancreatitis-related abdominal pain into short episodes/relapsing (type A), and constant/prolonged episodes of pain (type B), which is more common in alcoholic and early-onset idiopathic chronic pancreatitis.
- Steatorrhoea (common)
- Jaundice (uncommon): Due to common bile duct compression. Usually preceded by alkaline phosphatase elevation without jaundice or other symptoms. Pancreatic cancer should be considered.

OTHER DIAGNOSTIC FACTORS:

- weight loss and malnutrition (common)
- nausea and vomiting (common)
- skin nodules (uncommon): Pancreatic lipase may leak into the circulation and cause fat necrosis at non-pancreatic sites. This results in painful and painless skin nodules on the extremities, associated with fever and polyarthritis
- painful joints (uncommon): Occurs in at least 2 conditions associated with pancreatic disease: metastatic fat necrosis and IgG4-related autoimmune pancreatitis, associated with rheumatoid arthritis with or without secondary amyloidosis.
- low-trauma fracture (uncommon): Related to decreased bone mineral density, malnutrition, and increased systemic inflammation. Fracture risk is greater if alcohol is an underlying risk factor for chronic pancreatitis and patients have cirrhosis.
- abdominal distension (uncommon): Aetiology related to enlarged pseudocyst, pancreatic ascites due to juice leaking from a ruptured duct or pseudocyst, or duodenal fibrosis and obstruction leading to gastric distension and pancreatic cancer.
- shortness of breath (uncommon): Due to pleural effusion, secondary to juice leaking from a ruptured duct or pseudocyst and tracking to pleural space.

DIAGNOSTIC INVESTIGATIONS

1st investigations to order

Blood glucose	may be elevated
CT scan	pancreatic calcifications, focal or diffuse enlargement of the pancreas, ductal dilation, and/or vascular complications
Abdominal ultrasound	structural/anatomical changes including cavities; duct irregularity; contour irregularity of

	head/body; calcification
Abdominal X-ray	pancreatic calcifications

Investigations to consider

Endoscopic ultrasound (EUS) Helps to distinguish between chronic pancreatitis and intraductal neoplasms based on imaging features and the use of fine-needle aspiration, but EUS is imperfect	ductal and parenchymal abnormalities
endoscopic retrograde cholangiopancreatography (ERCP)	characteristically shows beading of the main pancreatic duct (from alternating dilation and stenosis) as well as irregularities in the side branches.
magnetic resonance cholangiopancreatography (MRCP) Excellent agreement with ERCP for severe chronic pancreatitis associated with marked changes in the main pancreatic duct.	may show the characteristic beaded appearance of the pancreatic duct as well as larger calcifications
faecal elastase-1 An indirect pancreatic function test; reduced in severe disease to <200 micrograms/g. All indirect pancreatic function tests have relatively high sensitivity and specificity in severe chronic pancreatitis with malabsorption. All are inaccurate for diagnosing mild to moderate pancreatic insufficiency.	low
faecal fat This test is performed by administering 100 g fat per day and measuring the faecal fat excretion over 72 hours. Increased faecal fat over 7 g/day is a late-stage manifestation of chronic pancreatitis.	increased
Steatocrit A rapid gravimetric method to measure stool fat. Past studies reported that when performed on samples from a 72-hour stool collection, steatocrit is as sensitive and specific as a 72-hour quantitative stool fat, and may be as accurate if performed on a 24-hour stool collection	increased
direct pancreatic function tests Pancreatic juice is collected with a gastroduodenal tube during exogenous hormone stimulation with cholecystokinin (CCK) and/or secretin. One major concern with recent "simpler" endoscopic methods is that these tests do not aspirate gastric juice to prevent degradation and/or dilution of pancreatic juice lipase and bicarbonate, which leads to false positive tests. Helps to differentiate pancreatic from non-pancreatic types of malabsorption.	decreased function
genetic screening	PRSS1; SPINK1; CFTR

biopsy	increased connective tissue, inflammation, fibrosis, loss of acini, protein plugs in ducts
IgG4 levels	positive in autoimmune pancreatitis
therapeutic trial of corticosteroids	positive response in autoimmune pancreatitis

Emerging test

investigational pancreatic function tests Newer methods of quantifying pancreatic exocrine function remain under investigation, including endoscopic pancreatic function tests, secretin-stimulated MRCP (SS-MRCP), and diffusion-weighted MRCP (DW-MRCP)	abnormal exocrine function

Table I. Differentiating features of chronic pancreatitis and other similar diseases

Disease	**Features allowing differentiation from chronic pancreatitis**	**Comments**
Pancreatic cancer and IPMN	Abdominal pain and substantial weight loss very common in those with malignancy. Less commonly present with exocrine insufficiency. Jaundice much more common than chronic pancreatitis. New onset diabetes relatively common in patients with pancreatic adenocarcinoma. Imaging studies may demonstrate mass lesions or pancreatic ductal dilation but usually not pancreatic calcifications. More likely to have elevations in CA 19-9. IPMN may have more diffuse and severe pancreatic duct dilation and at endoscopy may have a massively dilated pancreatic duct orifice filled with gelatinous mucin.	Chronic pancreatitis is a risk factor for pancreatic cancer and the 2 conditions may coexist. It can be very difficult to identify the presence of malignancy in some patients due to overlap in clinical characteristics and imaging features. EUS usually helpful in identifying underlying malignancy.
Biliary tract disease, including sphincter of Oddi dysfunction	Elevations in liver chemistries more common than in chronic pancreatitis. Pain more likely to be episodic and felt in RUQ. Imaging studies demonstrate normal-appearing pancreas and may identify abnormalities (e.g., dilatation) of biliary system.	Chronic pancreatitis can cause distal biliary obstruction. Autoimmune pancreatitis can also cause more proximal biliary tract strictures.
Chronic intestinal obstruction and ischemia	Pain usually only post-prandially and usually lasts for hours. Nausea and vomiting more prominent than chronic pancreatitis. Imaging studies during episode may show dilated small bowel. Imaging studies of abdominal vessels show disease in at least 2 of 3 major arterial systems (celiac, SMA, IMA).	Both intestinal obstruction and infarction can cause elevations in amylase and lipase.

Disease	Features allowing differentiation from chronic pancreatitis	Comments
Gastrointestinal motility disorders: gastroparesis and others	Pain usually more episodic than continuous. Nausea, vomiting, bloating, distension more common than in chronic pancreatitis. Imaging studies may note gastric distension or retained gastric contents. Abnormal motility study (e.g., gastric emptying study).	Gastroparesis and intestinal dysmotility syndromes can cause mild elevations in amylase and lipase. Patients with chronic pancreatitis often have coexistent gastroparesis.
Functional abdominal pain syndromes	Pain may be indistinguishable. Weight loss uncommon. Do not develop endocrine or exocrine insufficiency.	Most common situation in which chronic pancreatitis is misdiagnosed.
Abdominal wall (somatic) pain	Pain is sharper in character, associated with dysesthesias. Pain made worse by movement. Pain usually dermatonal in distribution.	May be due to both abdominal wall conditions (e.g., radiculopathy) or disease affecting peritoneal surfaces (e.g., adhesions or endometriosis).
Small bowel bacterial overgrowth	Diarrhea and bloating more common than in chronic pancreatitis, pain usually less pronounced.	Patients with chronic pancreatitis can frequently develop concomitant small bowel bacterial overgrowth.

Ammann's criteria (Zurich workshop) for diagnosing chronic pancreatitis

Recurrent pancreatitis plus 1 of the following:

- Calcifications
- Moderate or severe ductal lesions as defined by the Cambridge criteria
- Typical pancreatic histology
- Persistent exocrine insufficiency (2 years or longer).

Mayo Clinic diagnostic scoring system for chronic pancreatitis

Diagnosis is based on a total score of 4 or more derived from morphological and functional criteria (scores are in brackets):

- Pancreatic calcification: definite (4) or probable (2)
- Histology: definite (4) or probable (2)
- Steatorrhoea or lipase output less than 2 standard deviations below mean normal value: determined for each laboratory (2)
- Pancreatic duct abnormalities at endoscopic retrograde cholangiopancreatography (ERCP), CT, magnetic resonance cholangiopancreatography (MRCP) Cambridge classification I to III (3)
- Major clinical criteria: upper abdominal pain or weight loss over 10 kg in 12 months (2)
- Diabetes (fasting glucose >140 mg/dL) (1).

Mayo Clinic criteria for autoimmune pancreatitis

The Mayo Clinic proposed diagnostic criteria for autoimmune pancreatitis based on the acronym HISORt (Histology, Imaging, Serology, Other organ involvement, Response to therapy). Diagnosis requires at least 1 of the following sets of findings:

- Diagnostic histology
- Characteristic imaging on computed tomography and pancreatography (Narrowing of main pancreatic duct with irregular wall AND Diffuse or localised enlargement of the pancreas) with elevated serum IgG4 level
- Response to corticosteroid therapy of pancreatic/extrapancreatic manifestations of autoimmune pancreatitis (AIP).

MANAGEMENT step by step

1-st line:

1. alcohol and cigarette smoking cessation with lifestyle modifications
2. adjunct **analgesia**: Non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants or anticonvulsants, and opioids are commonly prescribed for the management of pain in this population. Increasingly, antidepressants, particularly tricyclic antidepressants, are prescribed to treat chronic pain syndromes. Tramadol has fewer GI side effects compared with morphine. The greatest adverse effect of opioids is addiction. Treatment of chronic pain with pregabalin (a gabapentoid effective in treating centralised neuropathic pain of other causes) has produced better pain reduction than placebo in painful chronic pancreatitis, although it is not yet licensed for such use.

Primary options

paracetamol: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

and/or

ibuprofen: 400-800 mg orally every 6-8 hours when required, maximum 3200 mg/day

AND

tramadol: 50-100 mg orally (immediate-release) every 4-6 hours when required, maximum 400 mg/day; 100 mg orally twice daily or 150 mg once daily initially (extended-release), increase when required, maximum 400 mg/day

Secondary options

desipramine: 10 mg orally four times daily, increase gradually according to response, maximum 300 mg/day

OR

morphine sulphate: 5-20 mg orally (immediate-release)/subcutaneous/intramuscular every 4 hours when required; 2.5 to 5 mg intravenously every 4 hours when required

OR

pregabalin: 50 mg orally three times daily initially, increase gradually according to response, maximum 300 mg/day; consult specialist for further guidance on dose

3. adjunct **pancreatic enzymes plus proton-pump inhibitor**
4. adjunct **dietary modifications**(a low-fat diet) **+ enteral feeding**
5. adjunct **octreotide :** 50 micrograms subcutaneously once or twice daily initially, increase according to response, usual dose 200 micrograms subcutaneously three times daily; 20 mg intramuscularly (long-acting) every 4 weeks; patient should be stabilised on subcutaneous formulation before switching to intramuscular formulation
6. adjunct **antioxidants**

If pancreatitis with pseudocysts – adjunct **pseudocyst decompression**(drainage can be done surgically, endoscopically, or percutaneously.)

- with biliary complications – adjunct **biliary decompression**(considered if 2-fold elevation in alkaline phosphatase persists for more than 1 month,and after excluding other causes of cholestasis (e.g., parenchymal disease, abscess).

N.B. The management of **diabetes** in patients with chronic pancreatitis is challenging. Patients are at risk for hyperglycaemia without treatment, but insulin therapy may cause insulin-induced hypoglycaemia due to glucagon deficiency. Experts recommend consuming small, frequent meals, receiving adequate pancreatic enzyme therapy, monitoring blood glucose, avoiding alcohol, minimising high-sugar foods or liquids, and consulting with a dietician.

SURGICAL MANAGEMENT

Major goals of surgery are to:

- Eliminate or reduce intractable pain
- Address associated complications: for example, biliary obstruction, duodenal obstruction, and pseudocyst compression
- Exclude pancreatic carcinoma
- Conserve functional tissue.

Historical predictors of surgical success are:

- Segmental fibrosis (distal or proximal)
- Diffuse ductal dilation (length >10 cm and diameter >5 to 7 mm)
- Associated or adjacent organ complication: for example, biliary obstruction, duodenal obstruction, and pseudocyst compression.

New predictors of surgical pain relief by multivariate analysis are:

- Onset of symptoms less than 3 years
- No pre-operative use of opioids
- 5 or fewer endoscopic procedures pre-operatively.

FOLLOW-UPto monitor for specific complications:

- Cholestasis and biliary obstruction (LFTs)
- Malnutrition: albumin, total protein, prothrombin time/INR, FBC, beta-carotene (Vitamin A), zinc, selenium, vitamin E
- Baseline bone densitometry in high-risk patients (i.e., post-menopausal women, men over the age of 50 years, previous history of low-trauma fracture) and patients with malabsorption. Surveillance exams should be offered in 2 years if osteopenia is detected. Those with osteoporosis should start appropriate medications and/or see a bone specialist.
- Steatorrhoea (qualitative faecal fat)
- Diabetes (glucose).

Complications associated with chronic pancreatitis

Complication	**Relative frequency or risk**	**Clinical considerations**
Exocrine insufficiency	Typically occurs after 5-10 years of disease but may occur earlier in conditions that cause obstruction of the pancreatic duct. Ultimately, approximately 70% of patients will develop exocrine insufficiency after 10 or more years of disease.	Diarrhea may not be present despite massive steatorrhea.Fat-soluble vitamin deficiency is common, especially vitamin D.
Endocrine insufficiency	Typically occurs after 5-10 years of disease. Ultimately, approximately 50-60% of patients will develop endocrine insufficiency after 10 or more years of disease. Patients may develop type II diabetes earlier (as a consequence of obesity and metabolic syndrome, not chronic pancreatitis).	These patients can be at high risk of treatment-induced hypoglycemia, which can be fatal.Pancreatic cancer may mimic the imaging features of chronic pancreatitis and also cause new-onset diabetes.
Secondary pancreatic carcinoma	The overall lifetime risk in patients with chronic pancreatitis is 3-4%.In patients with hereditary pancreatitis, the risk is quite substantial and may approach a lifetime risk of 70% in those with a paternal inheritance pattern.	Can be difficult to identify pancreatic cancer in the midst of a diseased pancreas. Serum CA 19-9 can be helpful but can be falsely elevated in patients with biliary obstruction and patients with pancreatitis. EUS is usually the most accurate way to identify mass lesions and sample them with FNA cytology. Surveillance programs

Complication	Relative frequency or risk	Clinical considerations
		(e.g., yearly CA 19-9 and EUS) are ineffective, except perhaps in those with hereditary pancreatitis. Prophylactic total pancreatectomy can be considered in some patients with hereditary pancreatitis.
Pancreatic pseudocysts	These occur in around 25% of patients with chronic pancreatitis.	Pseudocysts and cystic neoplasms of the pancreas have similar appearances but can be differentiated by historical features of the patient, usually complemented by EUS with FNA of the fluid.Pseudocysts may cause pain, obstruct a surrounding organ (stomach, duodenum, colon, or bile duct), become infected, or bleed. Symptomatic or complicated pseudocysts require therapy, which can include endoscopic, radiologic, or surgical drainage, depending on local expertise and location of pseudocyst.
Gastrointestinal bleeding	Chronic pancreatitis may cause bleeding by producing thrombosis of the splenic vein or by causing a pseudoaneurysm to develop within a preexisting pseudocyst. These are rare occurrences in patients with chronic pancreatitis.	Splenic vein thrombosis produces a segmental portal hypertension that causes gastric varices in the absence of esophageal varices. Bleeding is rare despite these varices and only occurs in about 4% of those patients who develop splenic vein thrombosis. Splenectomy is curative.Pseudoaneurysms of visceral arteries can occur in those with preexisting pseudocysts. Bleeding can be massive. The diagnosis is usually obvious on a CT with IV contrast. Angiographic embolization of the pseudoaneurysm is the preferred approach.
Biliary obstruction	Occurs in about 10% of patients, from fibrous compression of the distal bile duct by the chronic pancreatitis.	Patients usually develop jaundice but abnormal liver chemistries and jaundice may also occur from coexistent liver disease (e.g., alcoholic hepatitis). The bile duct stricture develops in the distal bile duct as it passes through the head of the pancreas. Additionally, more proximal bile duct strictures may be

Complication	Relative frequency or risk	Clinical considerations
		seen in patients with autoimmune pancreatitis. Surgical biliary bypass is the most durable therapy but long-term (12 months) placement of multiple plastic biliary stents or large-caliber, fully covered metal biliary stents at ERCP can resolve some distal biliary strictures due to chronic pancreatitis.
Duodenal obstruction	Occurs in about 5% of patients.	Usually occurs in those with large inflammatory mass of the head of the pancreas and often have coexistent biliary obstruction and relatively high-grade pancreatic duct obstruction. This same pattern can be seen in those with pancreatic adenocarcinoma of the head of the pancreas. Surgical therapy is generally required, often with resection of the pancreatic head.

4. **Equipment:** study room, ultrasound system "Mylab Six CristaLine". Students acknowledge with protocol and procedure of pancreas investigation, visit functional department (1st floor in University Clinic). Results of these investigations are provided to applicants during lesson.
5. **Learning hours: 2** hours.

Plan of the lesson

I. Organizational moment (greetings, checking who is present on the lesson, announcing topic and goal of the lesson, motivating applicants to study the topic).

II. Control of basic knowledge (oral questioning, tests, checking of how clinical cases and workbooks are fulfilled).

2.1. Demands for applicants theoretical preparation

Applicant should know.

Didactic units list:

1. Chronic pancreatitis: definition.
2. Etiology, pathogenesis.
3. Classification.
4. Clinical features.
5. Criteria of diagnostics.
6. Differential diagnosis.
7. Complications of chronic pancreatitis.
8. Treatment approaches and strategies.
9. Prognosis for life, convalescence and work capacity.

Questions (tests, tasks, clinical situations) to test basic knowledge on the topic of the lesson:

Tests for self-control

1.A patient having a chronic pancreatitis for many years, was tested and an increase of sugar up to 6,8 mmol/l in blood was found. What can these changes are explained?

A. Intoxication syndrome.

B. Incretory insufficiency of a pancreas. +

C. Calcinosis of a pancreas.
D. Malabsorption and maldigestion syndrome.
E. Cachexia.

2. A woman, 42 y.old, entered the gastroenterological department with a chronic relapsing pancreatitis in an exacerbation stage, suffering from the disease for 3 years. But during a physical examination and by the data of US, a hepatosplenomegaly and ascites were found for the first time. With the appearance of what syndrome can the course of this disease explained?
A. Pain abdominal syndrome.
B. Endocrine damage syndrome.
C. Exocrine insufficiency syndrome.
D. Portal vein compression syndrome.+
E. Toxic syndrome.

3. A patient 42 y.o., having gallbladder disease in the history, began to have sudden pain in the left hypochondria, after meal, frequent watery stool, alternating with constipations, with undigested food in faces. Skin and visible mucous membranes are of regular color, T – $36,7^0$C, pulse – 68 bpm, BP – 130/80 mmHg, palpation – pain in the left hypochondria andepigastric region. Presence of what disease does these changes show?
A. Biliary pancreatitis. +
B. Exacerbation of chronic calculus cholecystitis.
C. Gastric ulcer.
D. Ulcer of duodenum.
E. Chronic colitis, exacerbation.

4. A patient 37 y.o., admittedto the gastroenterological department and had a diagnosis of a chronic pancreatitis, exacerbation. During the examination the patient was had a biochemical blood analysis for the exclusion of ferment's «deviation» into blood. Which of the given data reflects this process?
A. Serum elastase.+
B. Blood urea.
C. Blood creatinine.
D. Blood bilirubin.
E. Blood albumin.

5.A patient K., 56 y.old, is troubled by pains of left hypochondria after meal, frequent watery stool. What's the preliminary diagnosis can be given to the given patient?
A. Chronic gastritis, exacerbation.
B. Myocardial infarction.
C. Gastric ulcer, exacerbation.
D. Chronic pancreatitis, exacerbation. +
E. Chronic choletistitis, exacerbation.

6. 4 hours after having meals a patient with signs of malnutrition and steatorrhea experiences stomach pain, especially above navel and to the left of it. Diarrheas take turns with constipation lasting up to 3-5 days. Palpation reveals moderate painfulness in the choledochopancreatic region. The amylase rate in blood is stable. X-ray reveals some calcifications located above navel. What is the most likely diagnosis?
A. Chronic pancreatitis +
B. Chronic gastroduodenitis
C. Duodenal ulcer
D. Zollinger-Ellison syndrome
E. Chronic calculous cholecystitis

7. A 75 year old man who has been suffering from diabetes for the last six months was found to be jaundiced. He was asymptomatic except for weight loss at the rate of 10 pounds in 6 months. Physical examination revealed a hard, globular, right upper quadrant mass that moves during respiration. A CT scan shows enlargement of the head of the pancreas, with no filling defects in the liver. The most likely diagnosis is:

A. Carcinoma of the head of the pancreas +
B. Infectious hepatitis
C. Haemolytic jaundice
D. Malignant biliary stricture
E. Metastatic disease of liver

8. A 45 y.o. man has complained of having epigastric and right subcostal aching pain, indigestion, dark color of the urine and acholic stool, fever and significant weight loss for 1 month. On examination: jaundice, presence of Curvuasier's sign. US scan did notreveal stones in the gallbladder and choledochus. What is the most likely diagnosis?
A. Cancer of the pancreas head +
B. Gallbladder stones
C. Chronic pancreatitis
D. Chronic cholangitis
E. Chronic hepatitis

9. A 68 year old patient has been suffering from chronic pancreatitis for 35 years. During the last 5 years he has been observing abatement of pain syndrome, abdominal swelling, frequent defecations up to 3-4 times a day (feces are greyish, glossy, with admixtures of undigested food), and progressive weight loss. Change of symptom set is caused by joining of:
A. Exocrine pancreatic insufficiency
B. Endocrine pancreatic insufficiency
C. Syndrome of lactase deficiency
D. Irritable bowels syndrome
E. Chronic enterocolitis +

10. A 56 y.o. man, who has taken alcoholic drinks regularly for 20 years, complains of intensive belt pain in the abdomen. Profuse no formed stool 2-3- times a day has appeared for the last 2 years, loss of weight for 8 kg for 2 years. On examination: abdomen is soft, painless. Blood amylase – 120U/L. Feces examination-neutral fat 15 g per day, starch grains. What is themost reasonable treatment at this stage?
A . Pancreatine +
B. Contrykal
C. Aminocapron acid
D. Levomicytine
E. Imodium

III. Formation of professional skills, abilities:
3.1. content of tasks (tasks, clinical situations, etc.)
Case history #1
A 41-year-old alcoholic man has a 6-year history of recurrent attacks of pancreatitis characterised by epigastric pain radiating to the back. The initial attack required hospitalisation for severe pain, and clinical chemistry showed a >15-fold elevation in serum amylase and lipase. Subsequent attacks were less severe, managed primarily as an outpatient, and lasted less than 10 days, with long symptomfree intervals. After detoxification 6 months ago he had no further attacks, but has recently developed evidence of diabetes and steatorrhoea. Computed tomography imaging shows pancreatic calcifications but no cystic or mass lesions.
Task: Applicant should write diagnosis, plan of investigation, carry out differential diagnosis, prescribe treatment for these case histories.

3.2. recommendations (instructions) for performing tasks (professional algorithms, orientation maps for the formation of practical skills, etc.)
Professional algorithms.
XXV. Patient's examination.
During patient's examination students should keep such communicative skills:

1. Friendly face expression.
2. Kind voice tone.
3. Greetings, showing concern and respect about the patient.
4. Find out patient's complaints and anamnesis .
5. Explanation of specific actions (hospitalization, carrying out investigations) which are planned to be performed in the future.
6. Student should perform liver palpation and percussion.
7. Finishing of the talk.

XXVI. Patient's investigation algorithm.

1. It should be explained to patient which investigation will be held and indications for this investigation.
2. A doctor should receive patient's agreement on investigation.
3. A doctor should warn patient about possibilities of unpleasant feelings during investigation.
4. Results of investigation should be explained to a patient.
5. Liver function tests (ALT, AST, bilirubin, AP, GGT, albumin) should be done.
6. Amilase and lipase levels should be checked in the blood serum.
7. Blood glucose should be checked.
8. Fecal elastase-1 should be checked and feces examination should be done.
9. Transcutaneous abdominal ultrasound (US) may be used as an initial test.
10. If on the abdominal x-ray pancreatic calcifications are absent, a dedicated pancreas protocol computed tomography (CT; which involves a CT of the pancreas with a reconstruction of the images) is recommended.
11. If the diagnosis remains uncertain, referral to a gastroenterology consultant is recommended to consider additional testing including magnetic resonance cholangiopancreatography, endoscopic ultrasound (EUS) (sensitive but specificity uncertain), endoscopic retrograde cholangiopancreatography (ERCP) are recommended.

XXVII. Step-by-step algorithm of treatment.

1. A patient should informed be about necessity of the prescribed treatment.
2. Dosages, drugs intake regimens, duration of treatment, side effects of the prescribed therapy should be kindly explained to patient.
3. Acute, intermittent episodes of pain require conservative management along with adequate analgesia, consisting of paracetamol and ibuprofen in combination with tramadol.
4. Pain management: Tramadol seems to be the best oral analgesic based on one randomised controlled trial demonstrating analgesia comparable to morphine in patients with chronic pancreatitis, and was found to cause fewer gastrointestinal side effects.
5. Octreotide is a synthetic analogue of somatostatin that may relieve pain through antinociceptive activity in the spinal dorsal horn, inhibition of neurogenic inflammation and/or inhibition of cholecystokinin release and pancreatic secretion.
6. 5-component antioxidant cocktail (containing selenium, beta-carotene, vitamin C, vitamin E, and methionine) may reduce the frequency of pain.
7. Pancreatin is a recommended first-line supplement. It is combined with omeprazole.
8. Options for patients who remain symptomatic include increasing the dose, adding inhibitors of acid secretion.

3.3. requirements for students work results.

As a results of studying students must perform the following:

-possess skills of communication and clinical examination of a patient with chronic pancreatitis;

-collect data on patient complaints, medical history, life history;

-evaluate information about the diagnosis of chronic pancreatitis using a standard procedure, based on the results of laboratory and instrumental studies;

-determine the list of required clinical, laboratory and instrumental studies and evaluate their results;

- identify the leading clinical symptom or syndrome;
- establish the most probable or syndrom diagnosis;
-assign laboratory and instrumental investigations for patient;
-carry out differential diagnosis in chronic pancreatitis;
-establish preliminary and clinical diagnosis;
- determine the principles of treatment, diet regimen for the patient.

3.4. control materials for the final stage of the lesson.

Work 1

1. Collection of complaints, anamnesis, examination of a patients with chronic pancreatitis.
2. Detection of clinical and instrumental symptoms.
3. Grouping symptoms into syndromes.
4. Definition of the leading syndrome.
5. Interpretation of laboratory and instrumental data.
6. Carrying out a differential diagnosis.
7. Formulation of the clinical diagnosis.
8. Write a prescription list for patients diagnosed with chronic pancreatitis, which would include diet and prescribed drugs.
9. Determining of the disability degree.

Work 2.

Assignment of differentiated treatment programs according to the clinical protocol of medical care.

Work 3.

Work in the Internet, in the reading room of the department library with thematic literature.
The applicant fills in the protocol of the patient's examination. An example of the initial examination of the patient is attached.

The tests for self-control with standard answers.

1. A 48-year-old man complains of constant pain in the upper abdomen, predominantly on the left, which aggravates after eating, diarrhea, loss of weight. The patient has alcohol use disorder. Two years ago he had a case of acute pancreatitis. Blood amylase is 4 g/hour·l. Feces analysis: steatorrhea, creatorrhea. Blood sugar is 6,0 mmol/l. What treatment should be prescribed?

A. Panzinorm forte (Pancreatin)
B. Insulin C. Gastrozepin (Pirenzepine)
D. Contrykal (Aprotinin)
E. No-Spa (Drotaverine)

2. 4 hours after having meals a patient with signs of malnutrition and steatorrhea experiences stomach pain, especially above navel and to the left of it. Diarrheas take turns with constipation lasting up to 3-5 days. Palpation reveals moderate painfulness in the choledochopancreatic region. The amylase rate in blood is stable. X-ray reveals some calcifications located above navel. What is the most likely diagnosis?

A Chronic gastroduodenitis
B Chronic pancreatitis
C Duodenal ulcer
D Zollinger-Ellison syndrome
E Chronic calculous cholecystitis

3. A 56 y.o. man, who has taken alcoholic drinks regularly for 20 years, complains of intensive girdle pain in the abdomen. Profuse nonformed stool 2-3- times a day has appeared for the last 2 years, loss of weight for 8 kg for 2 years. On examination: abdomen is soft, painless. Blood amylase - 12g/L. Feces examination-neutral fat 15 g per day, starch grains. What is the most reasonable treatment at this stage?

A Aminocapron acid

B Contrykal
C Pancreatine
D Levomicytine
E Imodium

4. A patient is 65 y.o. He has been a smoker for 40 years. He has lost 10 kg during the last 3 months. Complains of pain in the epigastric area after taking meals, diarrhea, jaundice. Physical examination revealed enlarged, painless gallbladder. Feces are light-coloured andclay-like. Blood analysis revealed increased level of whole and direct bilirubin, alkaline phosphatase and glutaminepyruvate transferase. Clinical urine analysis showed positive bilirubin reaction and negative urobilinogene reaction. Where is the initial process that caused these changes?
A In duodenum
B In common bile duct
C In liver
D In pancreas
E In gallbladder

5. A 36-year-old alcoholic patient has cirrhosis and pancreatic insufficiency due to recurrent pancreatitis. He complains of night blindness, decreased ability to taste food, and dry skin with hyperpigmentation. These complaints suggest deficiency of:
A Manganese
B Copper
C Selenium
D Chromium
E Zinc

6. A 68 year old patient has been suffering from chronic pancreatitis for 35 years. During the last 5 years he has been observing abatement of pain syndrome, abdominal swelling, frequent defecations up to 3-4 times a day (feces are greyish, glossy, with admixtures of undigested food), progressing weight loss. Change of symptom set is caused by joining of:
A Exocrine pancreatic insufficiency
B Endocrine pancreatic insufficiency
C Syndrome of lactase deficiency
D Irritable bowels syndrome
E Chronic enterocolitis

7. A patient suffers from chronic recurrent pancreatitis with evident disturbance of exocrine function. After intake of rich spicy food and spirits his stool becomes fatty. Reduced production of what factor is the most probable cause of steatorrhea?
A Tripsin
B Lipase
C Acidity of gastric juice
D Amylase
E Alkaline phosphatase

8. A 45-year-old patient complains of pain in the epigastric region, left subcostal area, abdominal distension, diarrhea, loss of weight. He has been suffering from this condition for 5 years. Objectively: tongue is moist with white coating near the root; deep palpation of abdomen reveals slight pain in the epigastric region and Mayo-Robson's point. Liver is painless and protrudes 1 cm from the costal arch. Spleen cannot be palpated. What disease can be primarily suspected?
A. Chronic pancreatitis
B. Atrophic gastritis
C. Peptic stomach ulcer
D. Chronic cholecystitis
E. Chronic enteritis

9. A 64-year-old patient has been hospitalised with complaints of progressive jaundice that developed over 3 weeks ago without pain syndrome, along with general weakness, loss of appetite.

Objectively: temperature is 36,8°C, heart rate is 78/min., abdomen is soft and painless, peritoneum irritation symptoms are not detected, palpation reveals sharply enlarged tense gallbladder. What disease can be characterised with these symptoms?
A. Acute cholecystitis
B. Duodenal ulcer
C. Cancer of pancreas head
D. Chronic cholecystitis
E. Cholecystitis caused by lambliasis
10. A 48-year-old woman has been suffering from chronic pancreatitis for the last 7 years. Lately she has been noticing an increase in daily feces with foul smell, abdominal distention, gurgling. The patient complains of diarrhea, weakness, fatigability, loss of appetite, loss of weight. What syndrome can be suspected in this case?
A. Malabsorption
B. Irritable colon
C. Maldigestion
D. Exudative enteropathy
E. Endocrine gland failure

Standard answers: 1-A, 2-B, 3-C, 4-D, 5-E, 6-A, 7-B, 8-A, 9-C, 10-A

IV. Summarizing, announcing the final grade, announcing the task for the next lesson.
Recommended resources:
- Basic literature source:
1. Recommendations from the United European Gastroenterology evidence-based guidelines for the diagnosis and therapy of chronic pancreatitis // Pancreatology. – 2018; 18 (8):847-854. doi: 10.1016/j.pan.2018.09.016.

Appendix 1

Example of the primary examination of the patient
Passport data: name and surname, age
Complaints:
pain after eating in the upper abdomen with irradiation in the back, nausea, bitter taste in the mouth, flatulence, profuse pasty stools with greasy shine 3-4 times a day. Due to pain and loss of appetite during this time she lost 12 kg.
Anamnesis morbi
The patient is sick for 2 years, previously did not look for medical help, was not examined.
Anamnesis vitae
Living conditions are satisfactory. Botkin's disease, tuberculosis, sexually transmitted diseases, malaria denies.
Professional anamnesis: not burdened.
Hereditary history is not burdened.
Pave not been in contact with infectious patients for the last 3 days. He has not left the country in the last 3 years.
***Hereditary history**: not burdened*
Neurological history
At the time of examination signs of focal neurological symptoms were not detected.
***Allergic history**: not burdened*
Epidemiology
Tuberculosis, malaria, viral hepatitis, Botkin's disease, veneral disease, HIV, AIDS, pediculosis – denies.
***Oncoanamnesis**: denies.*

***Insurance anamnesis**: There is no need to issue a seak leave, for the last 12 months a seak leave document has not been issued in this regard.*
***Postponed operations**: denies.*
***Bad habits**: abuses alcohol for 5 years.*
Examination of organ systems:
GENERAL Condition: satisfactory
CONSCIOUSNESS: clear
Body shape: hypostenic
Fatness: low nutrition
POSITION OF THE PATIENT: active
BODY TEMPERATURE: 36.6 C. Signs of alcohol intoxication – yes.
SKIN: Skin of pale pink, clean. Tissue turgor is normal. Skin pigmentation: no. Rash: no; other changes in the skin: no.
Visible mucous membranes: normal
LYMPH NODES: not enlarged
THYROID GLAND: no pathology
Oncological examination was performed, no visual forms of oncopathology were detected
Cardiovascular system:
PERCUSSION OF THE HEART: the limits of relative cardiac dullness: right on the right edge of the sternum, upper -III rib on the left parasternalis line, left - 1 cm outward from the left mediaclavicularis line in the V intercostal space
HEART activity: rhythmic, heart rate - 74 per 1 min. Pulse 74 in 1 min. Heart tones: muffled
HEART MURMURS: no
EDEMA: no
BP 125 / 85 mm Hg
EXAMINATION OF ARTERIES: no pathology
VEIN STUDY: no pathology
RESPIRATORY SYSTEM:
BREATHING: no dyspnea at rest, RR 16 in 1 min.
Sputum: no
CHEST: cylindrical, not deformed. Intercostal spaces: NOT smoothed. Participation of additional muscles: no, RR – 16 in 1 min. SpO2 = 98%
Percussion over the lungs: clear lung sound.
PULMONARY AUSCULTATION: vesicular breathing over both lungs. Pleural friction noise - no
DIGESTIVE SYSTEM:
TONGUE: wet; covered with yelowish plaque.
Tonsils: not enlarged
STOMACH: participates in the act of breathing. No hernia. Pulsation in the epigastrium - no. Dilatation of the subcutaneous veins of the anterior abdominal wall – no
Palpation: pain on palpation of the epigastrium, hypochondrium and navel.
Pathological symptoms: not detected
Liver: not enlarged
Gallbladder: not palpable
Pancreas: head of pancreas slightly painful on palpation
Spleen: not palpable
PERCUTIONAL SOUND OVER THE ABDOMINAL CAVITY: not changed
FECES: pasty chair with a greasy sheen
URINARY SYSTEM:
Palpation of the kidneys: not palpable
Pasternatsky's symptom is negative on both sides.
Urination: free, painless, frequency per day: 3-4 times.
Urinary incontinence: no.

SENSES:
SIGHT: not violated (OU). There is no other pathology
HEARING: normal, no deafness, pain: no. Tinnitus: no.
Musculoskeletal system:
Pathology of the musculoskeletal system was not detected
On the basis of complaints, anamnesis, objective examination, it is possible to make a preliminary diagnosis:
Chronic pancreatitis, exacerbation
Plan of investigation*general blood test, general urine test, glycemia level (8.00, 13.00, 17.00, 21.00)*
Biochemistry: liver tests, glucose, transaminases, protein, lipid spectrum, coagulogram, amylase, AF, LDH, GGT, CPK, serum iron, calcium, CRP, blood lipase, elastase, trypsin, coprogram
ECG, FGDS, ultrasound, CT, MRI of the pancreas
Consultation with gastroenterologist.
Treatment plan
Diet.
Refuse to consume alcohol.
Drug therapy:
- Platyphyllin hydrotartrate 0.2% solution of 8 mg orally, three to four times a day for 3-5 days
- No-spa - 1 tab. x3 times a day for 3-5 days
- Omeprazole 20 mg - 1 tab. 40 minutes before meals 1 month
- Mezim-forte 10000 - 1 tab. x3 times a day during or immediately after meals for 1 month

Appendix 2

Tests of basic knowledge level in KROK format

Theme 26. Chronic pancreatitis

1. 4 hours after having meals a patient with signs of malnutrition and steatorrhea experiences stomach pain, especially above navel and to the left of it. Diarrheas take turns with constipation lasting up to 3-5 days. Palpation reveals moderate painfulness in the choledochopancreatic region. The amylase rate in blood is stable. X-ray reveals some calcifications located above navel. What is the most likely diagnosis?
A. Chronic pancreatitis
B. Chronic gastroduodenitis
C. Duodenal ulcer
D. Zollinger-Ellison syndrome
E. Chronic calculous cholecystitis
2. A 75 year old man who has been suffering from diabetes for the last six months was found to be jaundiced. He was asymptomatic except for weight loss at the rate of 10 pounds in 6 months. Physical examination revealed a hard, globular, right upper quadrant mass that moves during respiration. A CT scan shows enlargement of the head of the pancreas, with no filling defects in the liver. The most likely diagnosis is:
A. Carcinoma of the head of the pancreas
B. Infectious hepatitis
C. Haemolytic jaundice
D. Malignant biliary stricture
E. Metastatic disease of liver
3. A 45 y.o. man has complained of having epigastric and right subcostal aching pain, indigestion, dark color of the urine and acholic stool, fever and significant weight loss for 1 month. On examination: jaundice, presence of Curvuasier's sign. US scan did notreveal stones in the

gallbladder and choledochus. What is the most likely diagnosis?
A. Cancer of the pancreas head
C. Chronic pancreatitis
D. Chronic cholangitis
E. Chronic hepatitis
4. A 68 year old patient has been suffering from chronic pancreatitis for 35 years. During the last 5 years he has been observing abatement of pain syndrome, abdominal swelling, frequent defecations up to 3-4 times a day (feces are greyish, glossy, with admixtures of undigested food), and progressive weight loss. Change of symptom set is caused by joining of:
A. Exocrine pancreatic insufficiency
B. Endocrine pancreatic insufficiency
C. Syndrome of lactase deficiency
D. Irritable bowels syndrome
E. Chronic enterocolitis
5. A 56 y.o. man, who has taken alcoholic drinks regularly for 20 years, complains of intensive belt pain in the abdomen. Profuse no formed stool 2-3- times a day has appeared for the last 2 years, loss of weight for 8 kg for 2 years. On examination: abdomen is soft, painless. Blood amylase – 120U/L. Feces examination-neutral fat 15 g per day, starch grains. What is themost reasonable treatment at this stage?
A . Pancreatine
B. Contrykal
C. Aminocapron acid
D. Levomicytine
E. Imodium
6. A patient having a chronic pancreatitis for many years, was tested and an increase of sugar up to 6,8 mmol/l in blood was found. What can these changes are explained?
A. Intoxication syndrome.
B. Incretory insufficiency of a pancreas.
C. Calcinosis of a pancreas.
D. Malabsorption and maldigestion syndrome.
E. Cachexia.
7. A woman, 42 y.old, entered the gastroenterological department with a chronic relapsing pancreatitis in an exacerbation stage, suffering from the disease for 3 years. But during a physical examination and by the data of US, a hepatosplenomegaly and ascites were found for the first time. With the appearance of what syndrome can the course of this disease explained?
A. Pain abdominal syndrome.
B. Endocrine damage syndrome.
C. Exocrine insufficiency syndrome.
D. Portal vein compression syndrome.
E. Toxic syndrome.
8. A patient 42 y.o., having gallbladder disease in the history, began to have sudden pain in the left hypochondria, after meal, frequent watery stool, alternating with constipations, with undigested food in faces. Skin and visible mucous membranes are of regular color, T – $36,7^0$C, pulse – 68 bpm, BP – 130/80 mmHg, palpation – pain in the left hypochondria andepigastric region. Presence of what disease does these changes show?
A. Biliary pancreatitis.
B. Exacerbation of chronic calculus cholecystitis.
C. Gastric ulcer.
D. Ulcer of duodenum.
E. Chronic colitis, exacerbation.

9. A patient 37 y.o., admittedto the gastroenterological department and had a diagnosis of a chronic pancreatitis, exacerbation. During the examination the patient was had a biochemical blood analysis for the exclusion of ferment's «deviation» into blood. Which of the given data reflects this process?
A. Serum elastase.
B. Blood urea.
C. Blood creatinine.
D. Blood bilirubin.
E. Blood albumin.
10. A patient K., 56 y.old, is troubled by pains of left hypochondria after meal, frequent watery stool. What's the preliminary diagnosis can be given to the given patient?
A. Chronic gastritis, exacerbation.
B. Myocardial infarction.
C. Gastric ulcer, exacerbation.
D. Chronic pancreatitis, exacerbation.
E. Chronic choletistitis, exacerbation.