Ministry of Education and Science of Ukraine
V. N. Karazin Kharkiv National University

GOUT

Methodical recommendations
for the preparation of students of higher education in the 5th year
of study in the discipline
«Internal medicine. Module of Internal medicine»

Electronic resource

Kharkiv – 2024

UDC 616-002.78
G 69

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Approved for distribution in the Internet by the decision of the Scientific and Methodical Council of V. N. Karazin Kharkiv National University (Protocol № 9 of June 18, 2024)

G 69 **Gout** : methodical recommendations for the preparation of students of higher education in the 5th year of study in the discipline «Internal medicine. Module of Internal medicine» [Electronic resource] / compilers T. M. Tykhonova, M. Yu. Gorshunska, O. V. Al-Trawneh/ – Kharkiv : V. N. Karazin KhNU, 2024. – (PDF 36 c.)

Methodical recommendations outline the importance of uric acid metabolism in the pathogenesis of gout, provide modern international definitions and classifications, consider the features of etiology and pathogenesis, clinical picture, diagnosis and treatment of gout. For students of the 5th year to prepare for practical classes in the discipline «Internal medicine. Module of Internal medicine».

UDC 616-002.78

CONTENT

LIST OF CONVENTIONAL ABBREVIATIONS

GC_s	–	glucocorticoids
HU	–	hyperuricemia
OA	–	osteoarthritis
IL	–	interleukin
MP	–	medicinal products
MSU	–	monosodium urate
NSAIDs	–	nonsteroidal anti-inflammatory drugs
RA	–	rheumatoid arthritis
UA	–	uric acid
ULT	–	urolithiasis
USD	–	ultrasound diagnostics
DM	–	diabetes mellitus
CNS	–	central nervous system

1. BASIC KNOWLEDGE, SKILLS, ATTAINMENTS NECESSARY FOR STUDYING THE TOPIC

Previous disciplines	Acquired skills
Propaedeutics of internal medicine	Conduct a physical examination of patients, analyze the results of basic laboratory and instrumental research methods
Foreign Language	To be able to work with foreign literature to obtain data on modern methods of diagnosis and treatment of rheumatological patients
Medical informatics	Analyze the results of research, be able to evaluate and interpret the results of clinical research from information sources, have the ability to work with electronic databases
Human anatomy. Normal physiology	Know the normal structure, functions and regulation of the musculoskeletal system, understand and determine the relationship of its structure and function with other organs and systems of the human body
Pathological morphology	Know typical pathological processes: mechanisms of development, changes in the human body, compensatory reactions of the body. Describe and schematically represent the mechanism of development of typical pathological syndromes in metabolic and rheumatological diseases, justify pathogenetic approaches to drug therapy

1.1. The student should know

– pathogenesis and stages of gout development, risk factors for the deposition of monosodium urate crystals (MSU);
– value of disturbance of metabolism of monosodium salt of uric acid (UA) and the role of long-term hyperuricemia (HU) in the pathogenesis of gout;
– main risk factors and etiological factors, pathogenesis of gout;
– definition and classification of gout;
– features of the clinical course and diagnosis of gout.

1.2. The student should be able to

1. collect complaints, history of patients with gout;

2. perform an objective examination of a patient with gout;
3. diagnose gout using diagnostic criteria;
4. carry out a differential diagnosis of gout;
5. on the basis of these complaints, anamnesis, objective examination of the patient, laboratory and instrumental diagnostics, using diagnostic criteria, establish a clinical diagnosis of gout.

2. TOPIC CONTENT

2.1. Actuality of theme

Gout is a systemic metabolic disease of polymorphic etiology with a purine metabolism disorder and the development of an inflammatory reaction in the places of UA salt deposition. According to various sources, the prevalence rate among the population ranges from 1 to 10 % in economically developed countries. According to the gender distribution, the number of cases among men dominates. Diet and genetic polymorphisms of renal urate transporters are likely major factors in primary gout. Gout and HU are associated with metabolic syndrome, diabetes mellitus (DM), kidney and cardiovascular diseases.

Non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine are more recommended drugs in the treatment of acute attacks, in the presence of special indications – glucocorticoids (GCs).

A major pathogenetic role in the occurrence of acute gout belongs to interleukin 1β (IL), the blockade of which has a good therapeutic response.

Patient education, appropriate lifestyle recommendations, and treatment are essential components in the management of patients with gout.

2.2. Definition of «gout». Epidemiology and etiology of gout

Gout (Latin podagra: pos, podis – leg, agra – trap – «leg in a trap») – a systemic disease that develops due to inflammation in places of deposition of MSU crystals in people with HU (UA concentration in serum > 6 mg/dL (> 360 μmol/l, > 0.36 mmol/l)) caused by environmental factors and/or genetic factors. In adult men, the norm of UA content in the blood reaches 262–452 μmol/l, in women – 137–393 μmol/l. At the age of over 60, the norms change: in men – 250–476 μmol/l, in women – 208–434 μmol/l.

There are separate norms for children under 12 years old, as well as for elderly people aged 90 and over.

The prevalence of gout in the world ranges from 0.1 % to 10 %, with predominance in developed countries (European countries – 0.9–2.5 % of patients, USA – 4 %). The factor responsible for the crystallization of UA or MSU in the synovial fluid and tissues of individuals with HU remains unknown.

The inflammatory process in the joints caused by crystals can be acute or chronic. Recurrent episodes of acute arthritis (gout attacks) and transition of the process to a chronic state lead to progressive damage to articular cartilage and bones. MSU crystals are deposited in peri-articular tissues, auricles (tophus), urinary system (in the interstitial tissue of the kidneys, collecting tubes and ureters) and in many other tissues and organs.

Etiology of gout

Primary gout (genetically determined), pathogenetic mechanisms:

- metabolic (hyperproductive) – increased UA synthesis due to genetically determined disorders in the synthesis of enzymes involved in the resynthesis of nucleotides from purines (hypoxantyl-guanine-phosphoribosyl-transferase deficiency, increased activity of phosphoribosylpyrophosphatase) – characterized by high uraturia, normal clearance of UA;
- renal (hypoexcretory, about 90 %) – the inability of the kidneys to compensate for the urate load by increasing tubular excretion – low uraturia, low UA clearance are typical;
- mixed – combination of both mechanisms – characteristic normal or reduced uraturia, normal UA clearance are typical.

Secondary gout (a manifestation of other diseases or a consequence of the certain medications use), mechanisms of development:

1. Increased UA formation in:

- diseases accompanied by massive breakdown of nucleotides from cell nuclei (leukemia, myeloma, psoriasis, hyperparathyroidism, sarcoidosis);

- excessive consumption of food containing a lot of purines (causes an excess of substrate in the body for UA synthesis (fruit juices and drinks sweetened with corn syrup with a high fructose content).

2. Insufficient excretion of urate in the following cases:

- diseases and conditions that disrupt renal excretion (accumulation diseases, hypothyroidism, hyperparathyroidism, chronic renal failure, congestive heart failure, gestosis, keto- and lactic acidosis, lead intoxication, obesity and excessive consumption of fatty food (red meat, game, offal, molluscs, some large sea fish), alcohol abuse (strong alcoholic drinks, beer – being metabolized to lactic acid, prevents the excretion of urates);
- the use of drugs for which HU is a predictable side effect caused by competition with urates on the path of elimination: antituberculosis drugs (pyrazinamide and ethambutol); didanosine (used in HIV infection); cyclosporine (immunosuppressant); salicylates (in a dose of more than 2 g/day); nicotinic acid, inosine, isoprinosine (metabolized to nucleotides and further to UA); rutin (with long-term use can contribute to the formation of urates in the kidneys); sildenafil, statins, angiotensin-converting enzyme inhibitors; thiazide diuretics, cytostatics;
- arterial hypertension;
- chemotherapy and radiation therapy;
- the postmenopausal period in women (in the premenopausal period, female sex hormones increase the excretion of UA in the urine);
- old age.

2.3. Pathogenesis of gout

Crystallization of urates under conditions of a critical level of HU occurs mainly in poorly vascularized areas and tissues with a lower temperature and pH level.

UA crystals are phagocytosed by macrophages (monocytes), resulting in activation of the inflammasome (a cytoplasmic complex of proteins that leads to

the transformation of proinflammatory cytokines into their active state). To date, activation of 4 types of inflammasomes have been identified: NLRP1, NLRP2, AIM2, IPAF, as well as, caspase-1, IL-1β, which leads to the development of an inflammatory process in the places where UA crystals are deposited (synovitis with hyperemia, proliferation of synoviocytes, and lymphoid infiltration occur in the synovial membranes).

Through cartilage defects, UA passes into the subchondral bone, where, forming tophi (painless nodular formations of 5 mm to 10 cm in size, morphologically – accumulation of urate crystals surrounded by granulomatous tissue, which contains giant multinucleated cells), causes bone destruction (on radiographs in the form of round defects «punches»). In some cases, over time, tophi can become calcified and even ossified.

MSU crystals are triggers for:

- cytokines: IL -1α, -1β, -6, tumor necrosis factor;
- chemokines: IL-8;
- mini-molecules: prostaglandin, histamine;
- fatty acids, which act as a secondary signal and are necessary for the development of gouty arthritis;
- cyclooxygenase-2.

IL-1β plays a very important role in the development of gout:

- induces the release of chemokines by cells of the endothelium and synovium, which leads to the migration of neutrophils into the joint;
- promotes the release of acute-phase proteins by the liver (C-reactive protein, serum amyloid);
- induces fever and pain sensitization;
- induces proliferation, potentiates the activation of immune cells and the release of inflammatory molecules;
- induces bone resorption and cartilage destruction.

2.4. Classification of gout

1. *Etiopathogenetic characteristics:*

- primary;
- secondary;

2. *Variants of gout manifestation:*

- typical (classical) acute
- subacute
- rheumatoid
- pseudophlegmonous
- by type of infectious-allergic polyarthritis
- low-symptomatic periarthritic.
- psoriatic;
- asthenic;
- abortive;

3. *Periods:*

- premorbid (HU);
- intermittent;
- chronic.

4. *Variants of gout course:*

- mild (attacks 1–2 times a year, damage to 1–2 joints; no visceropathy and radiological signs of bone destruction);
- moderate severity (attacks 3–5 times a year, damage to 2–4 joints, moderate bone and joint destruction, small tophi, urolithiasis (ULT));
- severe (more than 5 attacks per year, multiple joint lesions, pronounced bone and joint destruction, large tophi, significant nephropathy).

5. *Phases:*

- exacerbation (active);
- remission (inactive).

6. *Systemic manifestations of gout (tophus disease):*

- *associated with the deposition of crystals in tissues:*

- joints (metatarsophalangeal and interphalangeal joint of the 1st toe; interphalangeal joint of the 3d toe; interphalangeal joints of the hand; knee joints, shoulder, hip joints; spine; sacroiliac joints);
- synovial membrane;
- auricle;
- skin;
- cartilages of the nose;
- less often in the aorta, myocardium, heart valves, larynx;
- epiphyses of bones;

- *associated with UA excretion:*
  - gouty nephropathy (collective concept, includes tophuses in the kidney parenchyma, urate stones, interstitial nephritis, glomerulosclerosis, arteriosclerosis with the development of nephrosclerosis and predominance of tubular function disorders);
  - gastropathy

7. Degree of functional insufficiency:

0 – the function is saved;

I – preserved professional ability;

II – lost professional ability;

III - lost ability to self-care.

2.5. Clinical presentation of gout

1. Premorbid period: usually asymptomatic increase in the blood level of UA, unpleasant sensations in the joint, general malaise, nervousness, dyspepsia, fever, chills.

2. Intermittent period: the first acute attack lasts 1–7 days. Often at night there is a sharp pain in the first metatarsophalangeal joint, its swelling, fever. Also affected: metatarsophalangeal, metatarsal, less often knee joints. Objectively: disfigurement of the joint due to synovitis and swelling of soft tissues, the skin is

tense, stretched, pressure does not leave a pit. A change in skin color from purple to purple-cyanotic is typical. The boundaries of hyperemia are unclear, surrounded by a narrow strip of white skin. Then the local inflammatory phenomena are significantly reduced, the pain continues at night. After 5–6 days, the signs of inflammation gradually subside and disappear completely within the next 5–10 days.

In the early stages, most patients have repeated attacks 1–2 times a year. In the next period, acute attacks are repeated at different intervals, capturing an increasing number of joints of the legs and arms.

3. Chronic - develops from 2 to 30 years after the first attack. It is characterized by the formation of tophi, damage to joints and internal organs. The initial symptom of chronicity is a feeling of stiffness in the joints, which occurs after a state of rest. Later, permanent deformation of the joint appears, its stiffness increases, which is due to the destruction of the joints by urates and the development of secondary osteoarthritis. A feature of chronic gouty polyarthritis is a relatively small local soreness, while the mobility of the affected joints remains. Chronic gout leads to the development of ULT, later to other variants of gouty kidney.

Gout status – a severe course, characterized by continuous attacks of arthritis for several months in one or more joints against the background of constant inflammation (Fig. 1).

Inflammation

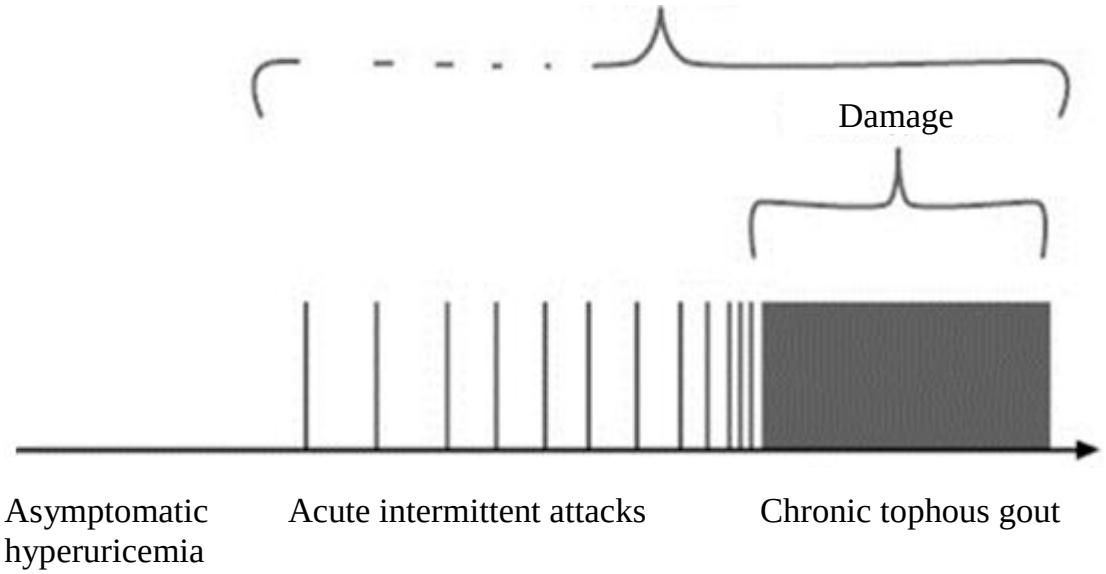


Fig. 1. Development and course of gout

Nephropathy in gout

Kidney damage occupies an important place in the gout clinic. Both HU and gout are associated with the development of urate nephrolithiasis. Damage to the kidneys in gout is conditionally divided into those caused by HU itself and crystal formation, and is also an attribute of concomitant diseases.

Risk factors for urate nephrolithiasis include:

1. *hyperuricosuria*, the reasons for which are:

– uncontrolled type 2 diabetes (high hyperglycemia);

– Lesch-Nyhan syndrome (a hereditary disease characterized by an increase in the synthesis of UA (in children) and caused by a defect in the enzyme hypoxanthine-guanine phosphoribosyl-transferase, which catalyzes the reutilization of guanine and hypoxanthine – as a result, a larger amount of xanthine and, therefore, UA is formed;

– treatment with uricosuric agents (benzbromarone);

– myeloproliferative diseases and chemotherapy, which in some cases lead to an acute urate crisis in the absence of proper prophylaxis.

Up to 70 % of UA is excreted by the kidneys, 15–20 % by the intestines, the skin, hair and nails absorb the remaining volume. At the same time, UA is

completely filtered by the glomeruli, but 99 % is reabsorbed in the proximal tubules, and this is a genetically determined process. Thus, one of the classic factors of urate nephrolithiasis – hyperuricosuria – is not suitable for explaining nephrolithiasis in gout. With hypouricemic hyperuricosuria (defect of URAT1 transporter) –gout does not occur, because gout requires hyperuricemia (supersaturation of blood, not urine).

2. *A small amount of urine*- is not leading in gout, as gout is not accompanied by diarrhea (with the exception of undesirable phenomena resulting from the use of colchicine in high doses), as well as other types of fluid loss.

3. *Acid pH of urine:* UA is present in urine in two forms: soluble (urate – ionized form, not associated with transport proteins) and insoluble (UA itself). They are distinguished by only one hydrogen ion, which acquires the ability to combine with the soluble form at pH < 5.5. It is shown that the number of H+ ions is increased in patients with gout, which provides a prerequisite for an active connection with urates. A large number of hydrogen ions is associated with a defect in the excretion of ammonium (NH_4) (urinary buffer), which, in turn, can occur due to a defect in the synthesis of glutaminase and / or glutamate dehydrogenase, which metabolize glutamine into ammonium and α-ketoglutarate.

4. *Genetic determinants*: ZNF365 on chromosome 10q21-q22, SLC2A9 gene encoding URAT1.

5. *A number of symptom complexes and diseases* are associated with the development of nephrolithiasis (table 1).

Table 1

Low pH conditions accompanying gout

Accompanying conditions	Frequency in gout, %	Feature
Obesity	80	pH is inversely correlated with body weight

Insulin resistance	60	A decrease in ammoniogenesis and ammonium excretion, which leads to a decrease in pH
Type 2 DM	20	When type 2 DM is combined with gout, the risk of developing nephrolithiasis is higher
A diet rich in purines	100	Transient increase in UA excretion

2.6. Diagnosis of gout

Laboratory studies

1. *Blood:* hyperuricemia (in men > 7.0 mg/dL (0.42 mmol/l), in women > 6.0 mg/dL (0.36 mmol/l), increased acute phase indicators (sialic acids, fibrinogen, seromucoid, C-reactive protein), often hyperlipidemia, possible hyperglycemia, hypercreatinemia;

2. *Urine:* uricosuria (more than 750 mg in a urine sample collected per day), possible slight proteinuria, leukocyturia, microhematuria;

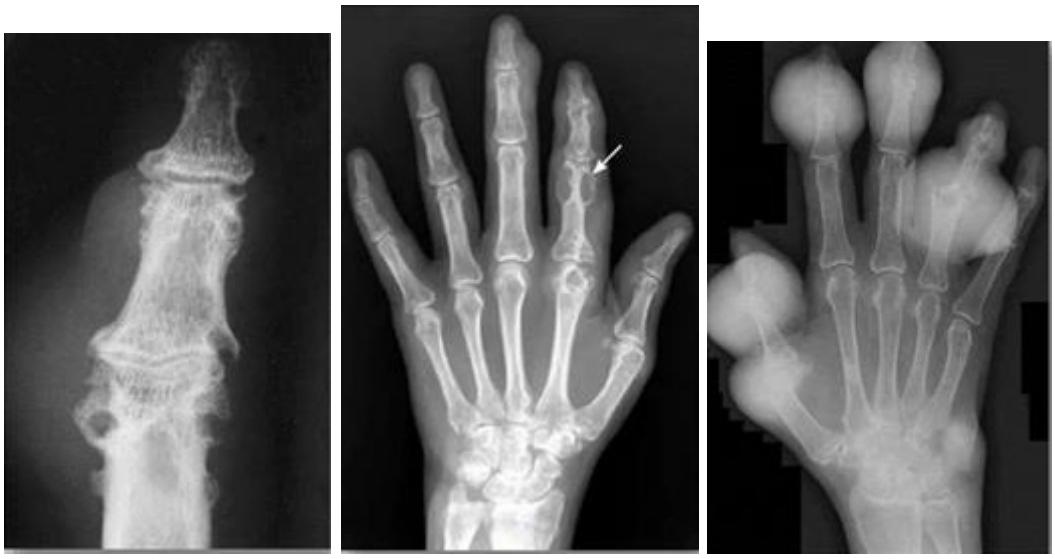
3. *Synovial fluid:* decrease in viscosity, high cytosis, needle crystals of MSU.

4. *Biopsy of* subcutaneous tophus, from fistulas that arise within tophus, or in the kidneys: identify MSU crystals that have the appearance of sticks or thin needles with broken or rounded ends about 10 μm long (the material must be fixed in absolute ethyl alcohol, since an aqueous solution of formalin, which is used in everyday practice, can dissolve crystals).

Radiography

With a chronic course – erosion of bone tissue or the symptom of a «puncher» (located in the epiphysis of the bones); sclerotic border and hanging edges («seagull wing» sign), which are formed during the destruction of the cortical substance; narrowing of the joint space.

X-ray changes are determined on average 5–7 years after the onset of gout, so they can be useful in verifying the diagnosis at later stages of the disease (Fig. 2).



Lithic erosions with overhanging margins | Symptom of a puncher | Gouty bone

Fig. 2. X-ray changes in gout

X-ray stages of joint damage:

I – large cysts (tophus) in the subchondral bone and in deeper layers, sometimes compaction of soft tissues;

II – large cysts near the joints and small erosions of the joint surfaces, constant compaction of peri-articular soft tissues, sometimes with calcifications;

III – large erosions of at least 1/3 of the articular surface, osteolysis of the epiphysis, significant compaction of soft tissues with lime deposits.

Ultrasound diagnostics

Urate deposits during ultrasound diagnostics (USD) can be detected in different ways: on the surface of the articular cartilage, it is visualized as a hyperechoic discontinuous strip that does not depend on the viewing angle (double contour effect), or in the joint fluid as floating hyperechoic heterogeneous cells that look like «snowstorm»; in the joint space or along the tendons in the form of hyperechoic aggregates suggest tofus. MSU crystals can also be visualized in the walls of blood vessels.

Computed tomography and magnetic resonance imaging

They provide information on the size of tophi, the presence of synovitis and joint damage, including bone erosion.

It is recommended to carry out a systematic examination of all patients with gout to detect concomitant diseases: obesity, renal failure, hypertension, coronary heart disease, heart failure, diabetes and dyslipidemia.

Gout classification criteria according to the American College of Rheumatology and the European League Against Rheumatism (ACR/EULAR,2015)

The EULAR/ACR gout classification criteria (Table 2) were developed for individuals with ≥ 1 episode (attack) of peripheral joint or synovial sac swelling, pain, or tenderness.

Table 2

Gout criteria, ACR/EULAR

Criterion	Category	Points
damage to joints or synovial bags during an attack (any time)	joint(s) or peri-articular bursa(s), except: ankle joint, metatarsal joint, 1st metatarsophalangeal joint (or their damage is exclusively a manifestation of polyarthritis)	0
	ankle joint or metatarsal joints (as a component of mono- or oligoarthritis) without damage to the first metatarsophalangeal joint	1
	first metatarsophalangeal joint (as a component of mono- or oligoarthritis)	2
clinical manifestations during an attack (any time)	erythema over the affected joint (from the patient's words or detected by the doctor)	1
	touching the joint or squeezing it is unbearable for the patient	1
	touching the joint or squeezing it is unbearable for the patient	1

continuation of table 2

Criterion	Category	Points
the course of the attack (any time); presence of ≥ 2 signs:	1 typical attack	1
	recurrent typical attacks	2

- time to the appearance of the maximum severity of pain < 24 hours; – disappearance of manifestations within ≤ 14 days; - complete reduction of symptoms in the period between attacks		
in the clinical picture of tofus	missing	0
	are observed	4
serum UA level (mg/dL [μmol/L])	< 4 (240)	-4
	From 4 to < 6 (from 240 to < 360)	0
	From 6 to < 8 (from 360 to < 480)	2
	From 8 to < 10 (480 to < 600)	3
	≥ 10 (600)	4
MSU crystals in the synovial fluid of a joint or periarticular bag with existing (ever) symptoms	No	-2
	the study was not conducted	0
	Yes	«+» diagnosis
MSU crystals in a joint or peri-articular bag with existing (ever) symptoms	a symptom of a double contour on ultrasound or urate deposits on computed tomography	4
joint damage associated with gout	≥ 1 erosion on x-ray of the hand or foot	4

The EULAR/ACR diagnostic criteria do not take into account the rapid resolution of the attack after taking colchicine (this symptom facilitates the diagnosis of the disease).

Interpretation of gout criteria (*ACR/EULAR):*

- ✓ sum of points ≥ 8;
- ✓ confirmed availability of MSU crystals in a symptomatic joint or synovial bag (i.e. joint fluid) or tophus (reliable criterion).

The gold standard of diagnosis- detection of phagocytosed MSU crystals in the synovial fluid of an inflamed joint, in the place of a synovial bag or tophus. Crystals can be detected using polarized light microscopy in patients with no definite diagnosis. It is possible to perform a joint puncture for diagnostic purposes in the acute and interictal periods.

Despite the fact that HU is the most important risk factor for the development of this disease, the serum level of UA is not a criterion for excluding or confirming gout: many patients with HU do not develop gout, and during an acute attack of the disease, the level of UA in blood serum can be normal or even reduced, that is, the diagnosis of gout should not be made in the presence of only HU.

If MSU crystals are not detected or if the study was not conducted, the following criteria are applied:

- clinical: typical attacks of gout, tophus;
- laboratory: UA concentration in serum;
- imaging: ultrasound, x-ray methods.

It is important to note:

- ✓ hyperuricemia ≠ gout;
- ✓ an increase in the level of UA in the blood can accompany various diseases or be a variant of the norm;
- ✓ the diagnosis is reliable in the presence of clinical and paraclinical (laboratory-instrumental) signs, and not only in the case of an increase in the UA blood level without clinical manifestations.

2.7. Differential diagnosis of gout

Gout attack: acute arthritis caused by calcium pyrophosphate crystals, hyperlipidemia, septic arthritis, reactive arthritis, trauma, hemarthrosis, serum sickness, early symptoms of other chronic arthritis, inflammatory response in osteoarthritis (OA).

Chronic gout: rheumatoid arthritis (RA), OA.

Characteristics of some nosological forms:

1. *Calcium pyrophosphate deposition disease*- can clinically mimic gout, often responds positively to NSAIDs and colchicine. The decisive factor is the

detection of calcium pyrophosphate crystals and a normal level of UA in blood serum during the analysis of joint fluid.

2. *Septic arthritis*- when the disease proceeds without fever or an increased level of leukocytes; arthrocentesis with further examination and culture of synovial fluid is crucial. Gout and septic arthritis can occur at the same time, but this is rare.

3. *Joint swelling associated with trauma* - is usually found in the anamnesis, but trauma can lead to exacerbation of gout due to an increase in the concentration of synovial urates. Imaging may be necessary to rule out a fracture in a patient with gout symptoms after a joint injury.

4. *RA* – positive rheumatoid factor (with seropositive RA), symmetric polyarthritis involving the proximal joints of the hand, small joints of the wrist and foot bones; osteoporosis with narrowing of joint spaces; erosion; subchondral cysts; subluxations; ankylosis.

5. *Psoriatic arthritis* – seronegative spondyloarthritis; asymmetric oligoarthritis; mutating arthritis; axial arthritis; it is not typical to involve carpometacarpal joints; «pencil-in-cup» symptom.

6. *Osteoarthritis* – the pains are mainly mechanical in nature (occur when the joints are loaded), the exacerbation of synovitis is milder than in gout, without significant swelling and hyperemia of the skin, there are no tophi, and there are no X-ray signs of gout.

2.8. Complications. Treatment of gout

Complications of gout

- severe degenerative arthritis;
- secondary infections;
- urate nephropathy;
- ULT;
- injury to nerve endings or spinal cord;

– fractures.

Treatment

When treating patients, the therapeutic goal is to reduce UA < 360 μmol (decrease to 420 μmol/l does not solve the problem, but only slows down the progression of the disease). Patients with concomitant diseases should have an even lower UA level. Because the lower the UA level, the faster the tophus decrease and the much faster dissolution of UA crystals is observed. And as a result, we can say that gout is one of the few arthritis that can be cured.

At the same time, it should be noted that an excessive decrease in the level of UA or its low level is a risk of developing degenerative-dystrophic processes of the central nervous system (CNS), such as Parkinson's disease, multiple sclerosis or Alzheimer's disease. It has been established that a high level of UA provides a neuroprotective effect in the CNS.

Pharmacotherapy

For the rapid and complete disappearance of symptoms of acute gout treatment, medicinal products (MP) should be started within 24 hours of the onset of symptoms (Figure 3, see page 26).

Oral and intravenous GCs, NSAIDs, and colchicine are equally effective in the treatment of acute gout attacks.

NSAIDs – are first-line drugs in the treatment of an acute gout attack. Indomethacin has historically been the preferred choice; however, there is no evidence that it is more effective than any other NSAIDs. The course of treatment is continued for an additional 1–2 days after the symptoms have disappeared.

GCs- patients with DM can be prescribed GCs for short-term use with appropriate monitoring of hyperglycemia. When gout is limited to one joint, intra-articular injections of GCs (hydrocortisone 25–100 mg) have the advantage of a lower side effect profile (but no more than one injection per 3 months in the same joint). After the gout attack is resolved, prophylactic use of GCs is recommended with a reduction in the daily dose for a total course of 10–14 days.

Colchicine – has the following reception scheme: 1 mg immediately and 0.5 mg after an hour, then 1.5 mg per day. Among the possible side effects: nausea, vomiting, diarrhea, axonal neuromyopathy, possible rhabdomyolysis when taken simultaneously with statins or clarithromycin. It should be used with caution in patients with hepatic or renal insufficiency and with simultaneous use with inhibitors of cytochrome P450, 3A4 or P-glycoprotein.

Urate-reducing therapy

According to the current EULAR recommendations from 2016, the indications for urate-lowering therapy are (Figure 4, see page 27):

– tofus;
– 2 arthritis in a year;
– one arthritis and more;
– a patient with the debut of gout at the age of less than 40 years;
– a patient with arthritis with a very high level of serum UA (more than 8 mg/dL or 480 μmol/L);
– a patient with concomitant diseases (chronic renal failure, arterial hypertension, coronary heart disease, heart failure)

Serum urate levels should be reduced to a target value of < 6 mg/dL (360 μmol/L). Normal serum urate levels do NOT exclude the diagnosis of gout. They should be monitored periodically to assess prophylactic therapy in patients with recurrent gout and a history of elevated urate levels. The duration of urate-lowering therapy lasts the entire life of the patient.

Allopurinol – a xanthine oxidase inhibitor, is a first-line agent for the prevention of gout relapses. In patients with gout and chronic kidney disease or congestive heart failure, allopurinol has the added benefit of preventing progression of the chronic disease. Start with 100 mg/day p/o, every 2–4 weeks. Increase by 100 mg to max. 600 mg/day; can cause hypersensitivity syndrome (fever, rash, hepatitis, eosinophilia, renal failure). Dosage is regulated by the target serum UA level. In patients with chronic kidney disease, low initial doses

with slow titration to achieve the target UA level are recommended. Doses above 300 mg may be used – even in patients with renal impairment – provided patients are closely monitored for adverse effects. Certain ethnic and racial groups (patients of Chinese, Thai, Korean, or African American descent) have a higher risk of severe cutaneous hypersensitivity reactions when initiating therapy with allopurinol. Therefore, it is recommended to screen for the genotype of the human leukocyte antigen HLA-B*5801 before starting treatment.

Febuxostat– xanthine oxidase inhibitor. It is also considered a first-line agent to prevent relapses of gout, but it is significantly more expensive than allopurinol. Initially 80 mg/day can be increased to 120 mg/day; it is metabolized in the liver – it can be used in patients whose degree of impaired kidney function does not allow an increase in the dose of allopurinol.

Probenecid (not registered in Ukraine) – a uricosuric drug – increases the excretion of UA in the urine and is usually used in second-line treatment due to numerous drug interactions (for example, when taken simultaneously with methotrexate or ketorolac, it significantly increases their concentration in the blood, which can lead to severe toxicity). Nephrolithiasis is a common side effect that can be avoided by drinking plenty of fluids and using potassium citrate, which helps alkalinize the urine. The recommended dose is 500 mg 1–2 times/day with subsequent dose titration. It is indicated for HU caused by impaired renal excretion of UA (< 700 mg/24 h); contraindications: age > 60 years, creatinine clearance < 50 ml/min, nephrolithiasis.

Pegloticase (not registered in Ukraine) – a strong urate-lowering drug for the treatment of refractory gout, including using a combination of a xanthine oxidase inhibitor and a uricosuric drug. Pegloticase metabolizes the conversion of UA into allantoin. This reduces the risk of sediment formation and gout development, as allantoin is 5–10 times more soluble than uric acid. Treatment regimen: 8 mg intravenous infusion once every 2 weeks for 12–16 weeks. Control of uric acid level before each infusion.

Canakinumab (not registered in Ukraine) – fully human IgG1/kappa isotype monoclonal antibody to IL-1β. Canakinumab binds to human IL-1β with high affinity, thereby preventing interaction of IL-1β with its receptors, IL-1β-induced gene activation, and production of inflammatory mediators. Indications: acute attack of gouty arthritis, prevention of new attacks in case of ineffectiveness, intolerance or in the presence of contraindications to the use of NSAIDs and/or colchicine and in the case of impossibility of therapy with repeated courses of GCs.

Diet for gout and hyperuricemia

Neutral risk:

– consumption of vegetables and unsweetened fruits (avocado, lime, lemon, cranberry, plum, strawberry, raspberry, grapefruit, watermelon, currant (red, white, black), nectarine);

– tea, juice (no more than 1 glass per day);

– sometimes beans, nuts;

Reduce the risk:

– use of healthy oils (olive, rapeseed) for cooking, for salads, etc.;

– drinking water, coffee without sugar;

– low-fat dairy products (2–3 servings per day);

– milk (1–2 servings per day);

– cherry juice;

– consumption of whole grain products (brown rice, whole grain bread and pasta);

Increase the risk:

– limit butter;

– exclude trans fats, fried potatoes, French fries (chips) from the diet;

– avoid drinking sweet drinks;

– limit the use of refined grain products (white rice, white bread);

– sometimes eat fish, poultry;

– limit red meat;
– exclude bacon, assorted meats and other meat products;
– limit / exclude alcohol (to a greater extent, beer, liquor).

Treatment of concomitant diseases

If possible, the patient should not take acetylsalicylic acid, as well as loop and thiazide diuretics, which increase the concentration of UA in the plasma.

Consider the use of MP that reduce the risk of flares in patients with gout: losartan or a calcium channel blocker during the treatment of arterial hypertension, as well as statins or phenobarbital during the treatment of hyperlipidemia.

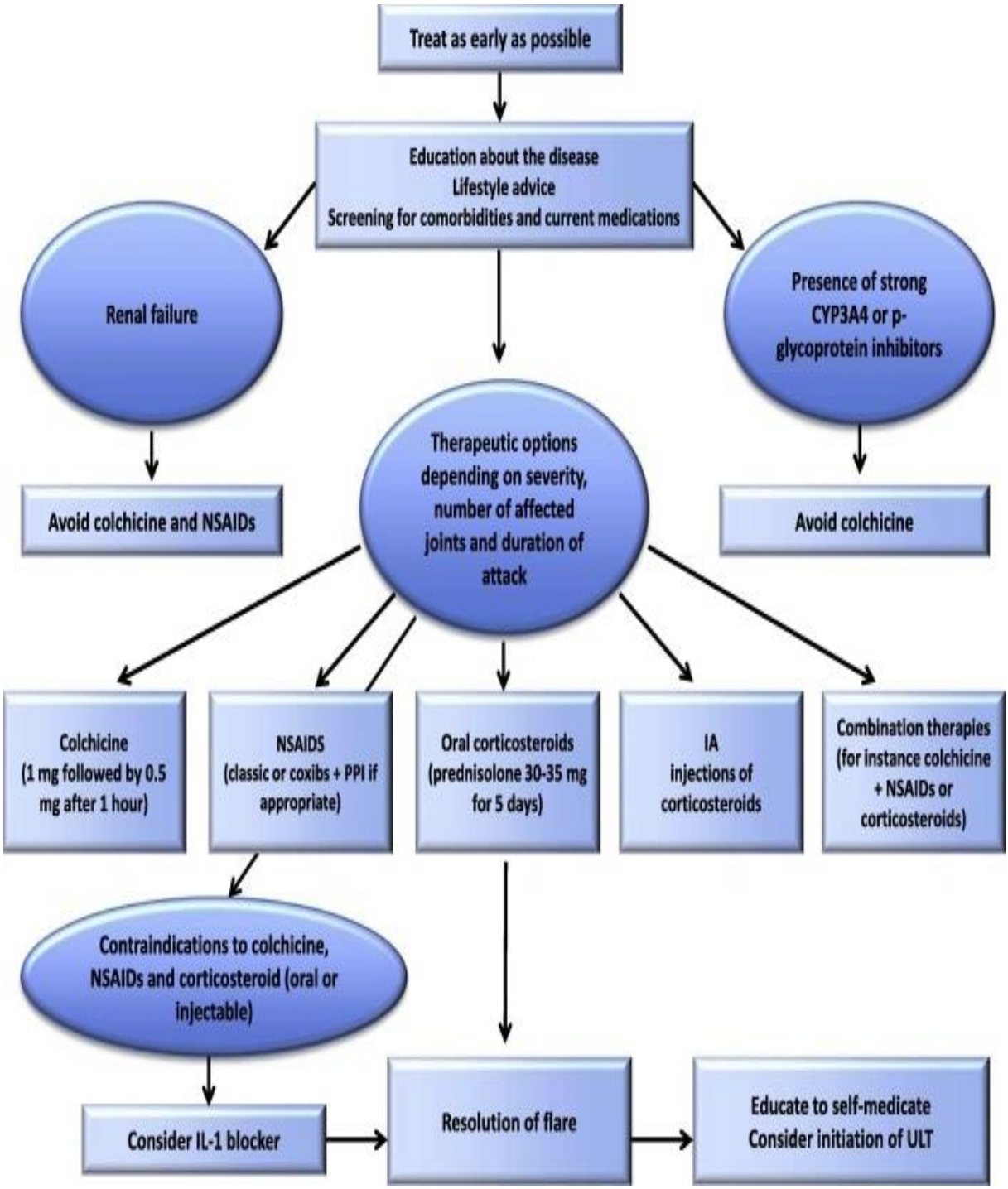


Fig. 3. EULAR recommendation for the management of flares in patients with gout.

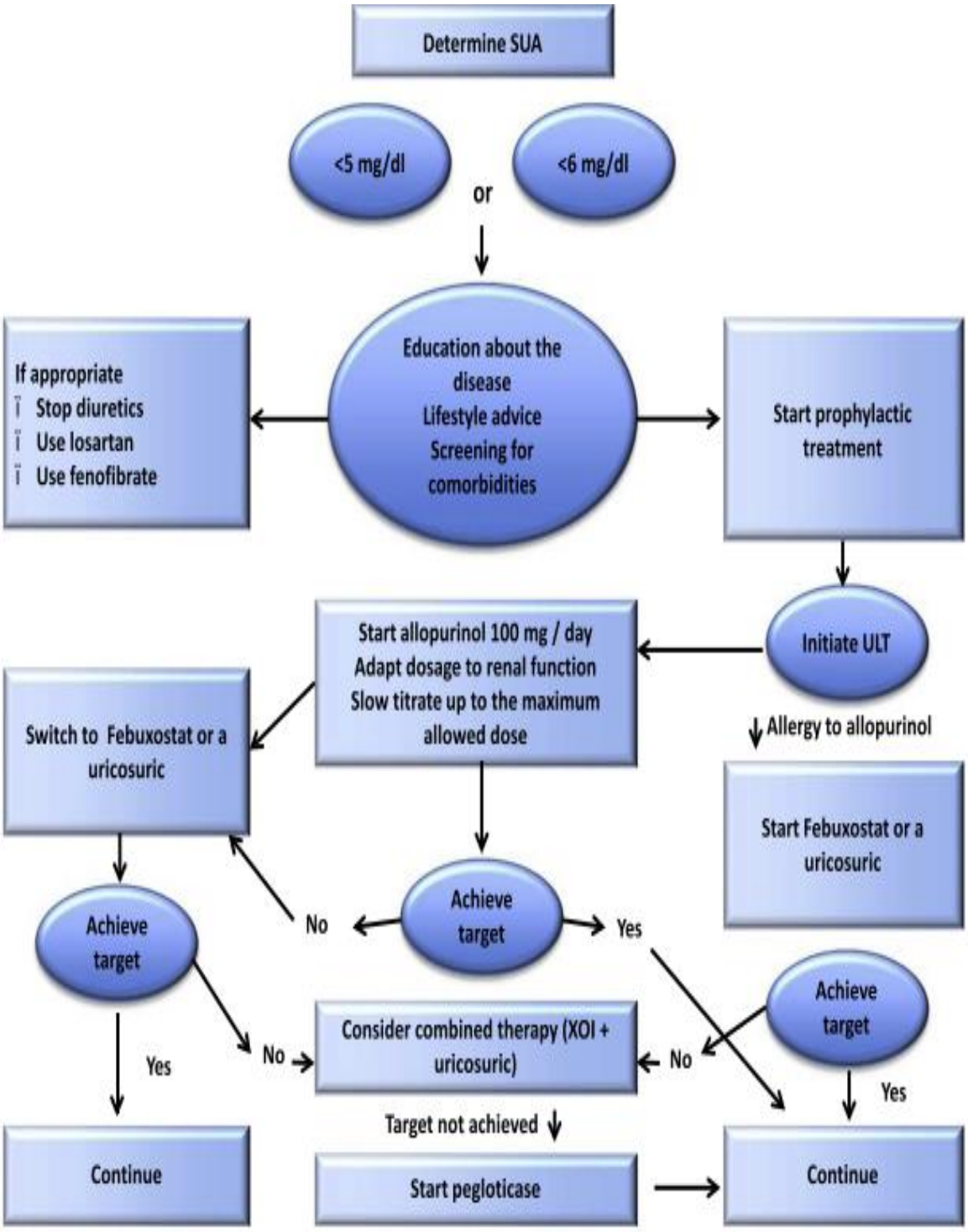


Fig. 4. EULAR recommendation for the management of hyperuricemia in patients with gout (SUA- serum uric acid, ULT –urate lowering therapy , XOI - xanthine oxidase inhibitor).

2.9. Prognosis and work capacity in gout

Exacerbation of gout leads to disability. But treatment of gout in the early stages has a good prognosis. However, relapses are relatively common in the first 6–24 months of treatment.

Prognostically unfavorable factors:

– age up to 30 years;
– persistent HU exceeding 0.6 mmol/l (3.6 mg/dL);
– persistent hyperuricosuria > 1100 mg/day;
– progressive nephropathy, especially in combination with DM and hypertension.

Importantly, HU and gout are associated with an increased risk of death. Life expectancy is determined by the development of renal and cardiovascular pathology. Analysis of nationwide data indicates that patients with gout have an increased risk of myocardial infarction and stroke. At the same time, uratereducing therapy ensures a reduction of these risks. Thus, it was demonstrated that the use of allopurinol and benzbromarone reduced the risk of death by 53 % and death from cardiovascular diseases by 71 %, in contrast to no treatment.

2.10. Examples of the diagnosis formulation

1. Acute gouty arthritis of the first metatarsophalangeal joint of the right foot, functional insufficiency of the joint, 2nd degree.

2. Chronic tophous gout, exacerbation. Arthritis of the left ankle joint and joints of the right foot, functional insufficiency of the joint, 3rd degree. Tubulointerstitial nephritis. Chronic renal failure, 1st stage.

TEST TASKS FOR SELF-CONTROL

1. Specify the level of UA in blood serum associated with an increased risk of gout:
   A. more than 6.0 mg/dL;
   B. more than 5.0 mg/dL;
   C. less than 6.5 mg/dc;
   D. less than 3.5 mg/dc.

2. What are the indications for allopurinol prescribing for gout?
   A. hyperproduction of urates (UA 800 mg in urine collected in 24 hours, with a normal diet);
   B. nephrolithiasis;
   C. renal failure (creatinine clearance 50 ml/min).
   D. tofus

3. Among the listed, which is NOT characteristic of hyperuricemia?
   A. urate nephropathy;
   B. uric acid nephropathy;
   C. urolithiasis with the formation of urate stones;
   D. polycystic kidney disease.

4. Which of the following corresponds to the clinical manifestations of gout?
   A. involvement of the metatarsophalangeal joint of the big toe in the pathological process;
   B. during an exacerbation, a sharp reddening of the skin over the affected joint;
   C. deformity of the joints;
   D. nephropathy, a possible attack of renal colic;
   E. subcutaneous nodules on the ears and elbows;
   F. all of the above.

5. A positive effect from regular oral administration of colchicine is a generally accepted diagnostic test for:
   A. rheumatoid arthritis;
   B. Bekhterev's disease;
   C. gout;
   D. reactive arthritis.

6. An acute attack of gout can be triggered by:
   A. hypothermia;
   B. abuse of alcohol and meat food;

C. long walking;
D. psycho-emotional stress;
E. all of the above.

7. What is the alternative for the treatment of acute gouty arthritis, if the patient is contraindicated to use drugs internally?

A. Indomethacin, 50 mg 3 times per day through a nasogastric tube;
B. Colchicine 2 mg in 20 ml of physiological solution of sodium chloride for intravenous administration for 20 minutes. May be repeated at a dose of 1 mg every 6 hours.
C. Drotaverin hydrochloride 40–80 mg IV slowly in an acute attack;
D. Electrophoresis with novocaine.

8. Which disease is characterized by the following criteria: recurrent typical attacks in the ankle joints or metatarsal joints, touching the joint or squeezing it is unbearable for the patient, UA level in the blood serum > 6 mg/dL, erosion of the joint surfaces on X-ray of the hand or foot?

A. rheumatoid polyarthritis;
B. osteoarthritis;
C. gout;
D. ankylosing spondylarthrosis.

9. For emergency care of a patient with an acute attack of gout, it is recommended to prescribe:

A. Drotaverin (No-shpa);
B. Colchicine;
C. Diclofenac;
D. applications of Dimexide;
E. antibiotics

10. On the X-ray there are «stamped» defects of the epiphyses. There is a history of acute pain in the first toe and knee joint after prolonged walking. It is more likely that the patient:

A. purine metabolism disorder;
B. disturbances of carbohydrate metabolism;
C. aseptic inflammation with purine metabolism disorder;
D. disturbances of electrolyte metabolism;
E. disturbances of pH-environment.

Keys:1 – A; 2 – A; 3 – D; 4 – F; 5 – C; 6 – E; 7 – B; 8 – C; 9 – B; 10 – C.

SITUATION TASKS

1. The patient, 45 years old, complains of sharp pains in the big toe of the left foot. During the examination, it is noted: the joint is enlarged in volume, bluish-red, t of the body – 38.5º C. Blood: leukocytes – $10.2x10^9$ /l, ESR – 34 mm/h. UA – 0.525 mmol/l. What is the diagnosis?

A. gouty arthritis;
B. psoriatic arthritis;
C. rheumatoid arthritis;
D. osteoarthritis;
E. reactive arthritis.

2. A 37-year-old patient developed sharp pains in the metatarsophalangeal joint of the left big toe after eating meat. Objectively: the skin over the affected joint is purplish-bluish in color, the patient cannot stand on his feet due to sharp pain. What is recommended to prescribe for emergency care?

A. Serratopeptidase (Serrata);
B. Etoricoxib (Arcoxia);
C. Colchicine;
D. Leflunomide (Arava);
E. none of them

3. A 55-year-old man was admitted to the clinic due to an attack of renal colic, which periodically recurs during the year. Objectively: in the area of the auricles and the right elbow joint there are nodular formations covered with thin shiny skin. Pulse – 88/min. Blood pressure – 170/100 mm Hg. Art. Positive Pasternatsky's symptom on both sides. The patient is scheduled for an examination. Which laboratory indicator is the most appropriate to investigate to establish a diagnosis?

A. uric acid;
B. rheumatoid factor;
C. ESR;
D. urine sediment;
E. lactic acid.

4. A 37-year-old patient suddenly developed severe pain in the metatarsophalangeal joint of the big toe at night after celebrating his birthday. The joint is bluish-purple, increased in volume. Body temperature – 38.8º C, leukocytes in the blood – 9.6×10^9/l, neutrophils – 74 %, ESR – 30 mm per hour. UA – 0.490 mmol/l. What is the diagnosis?

A. gouty arthritis;
B. purulent arthritis;

C. rheumatoid arthritis;
D. deforming arthrosis;
E. psoriatic arthritis.

5. A 30-year-old man complains of severe pain, «redness» of the skin, swelling in the area of the ankle joint, temperature rise to 39º C. He fell ill suddenly. In the past, there were similar attacks lasting up to 5–6 days without residual changes in the joint. The skin over the joint is hyperemic without clear contours and an infiltrative shaft on the periphery. What is the most likely diagnosis?

A. gout;
B. infectious arthritis;
C. rheumatoid arthritis;
D. erysipelas;
E. osteoarthritis.

Keys:1 – A; 2 – C; 3 – A; 4 – A; 5 – A.

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Електронне навчальне видання комбінованого використання
Можна використовувати в локальному та мережному режимі

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ПОДАГРА

Методичні рекомендації для підготовки
здобувачів вищої освіти 5-го року навчання з дисципліни
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(Англ. мовою)

В авторській редакції

Підписано до розміщення 18.06.2024. Гарнітура Times New Roman.
Ум. друк. арк. 2,05. Обсяг 0,655 Мб. Зам. № 167/24.

Харківський національний університет імені В. Н. Каразіна,
61022, м. Харків, майдан Свободи, 4.
Свідоцтво суб'єкта видавничої справи ДК № 3367 від 13.01.2009

Видавництво ХНУ імені В. Н. Каразіна