

A.S. Svintsitskyy

Bogomolets National Medical
University, Kyiv

GOUT: CURRENT DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS

Abstract

This paper presents the current views on the diagnosis, treatment and prophylaxis of gout, based on the latest Ukrainian and international guidelines.

Keywords

Gout, hyperuricemia, uric acid, classification criteria, diagnosis, treatment, prophylaxis.

Gout is a chronic metabolic disease caused by purine metabolism disorders [2, 3, 9, 23, 41].

Epidemiology. Prevalence of hyperuricemia (HU) in the world is 2-12%. Approximately 1-2% of adult population have gout, mainly males aged after 40 years. In females disease starts after menopause. Male/female ratio is 7-10:1, but in patients over the age of 65 this ratio is reduced to 3-4:1 [15, 40, 44].

Etiology. Gout is a multifactorial disease. Its onset is associated with genetic susceptibility and the influence of dietary and environmental factors [30]. Genetic studies have identified association between single-nucleotide polymorphisms in some genes (URAT1/SLC22A12, GLUT9/SLC2A9, ABCG2/BCRP, SLC22A11/OAT4, SLC17A1/NPT1, SLC17A3/NPT4) and serum uric acid (UA) concentrations [21, 34, 36].

Excessive purine intake (red meat, fish, beans), alcohol (wine, beer, liquor) abuse and physical inactivity promote gout development. An increased synthesis of UA and reduced its excretion are the causes leading to the urates accumulation.

Pathogenesis. Gout is divided into primary and secondary. Main pathogenic mechanisms of primary gout development are:

- metabolic (it is caused by UA synthesis increase as a result of genetic abnormalities in the enzymes synthesis, first of all the functional insufficiency of hypoxanthine guanine phosphoribosyltransferase, involved in resynthesis of purine nucleotides, and the increased activity of phosphoribosyl pyrophosphate-synthetase);
- renal (it is associated with a decreased excretion of UA by the kidneys without pathological changes in them);

- mixed (it is characterized by a combination of both mechanisms) [11, 29, 43].

Development of secondary gout, as well as primary, may be caused by increased formation of UA and slowing of its excretion. Increased synthesis of UA is observed in polycythemia vera and secondary erythrocytosis, acute and chronic leukemias, myeloma, psoriasis, excessive consumption of purine rich foods, alcohol abuse, use of fructose containing products. Insufficient urate excretion is observed in chronic kidney disease, lead-induced nephropathy, keto- and lactoacidosis, dehydration, use of diuretics (mainly thiazide), cytostatic drugs, ethambutol, etc. [43, 45, 52].

Attack of gouty arthritis develops due to the formation of monosodium urate (MSU) crystals in the joint. Adsorbed on crystals IgG reacts with Fc-receptors on the cells of inflammation, activating them, and apolipoprotein B, which is also a part of protein membrane of urates, inhibits phagocytosis and cell immune response.

Phagocytosis of crystals causes the release of various proinflammatory substances (collagenase, glucuronidase, neutral protease, etc.), cytokines (IL-1, IL-6, IL-8, TNF- α), prostaglandins, kinins, toxic radicals, activation of Hageman factor and system complement, leading to increased vascular permeability, neutrophil migration, nonspecific acute synovitis.

The phenomenon of proliferation, lymphoid infiltration of synovial membrane prevail in case of chronic arthritis. The MSU crystals penetrate the cartilage and synovial membrane, where they accumulate in the needle-like form. Urates penetrate the subchondral bone through cartilage defects, and forms tophi, that cause bone destructions [7, 12, 13].

Table 1. Clinical classification of gout [4]

Clinical stages	1) acute gouty arthritis; 2) interval gout; 3) chronic gouty arthritis (exacerbation, remission); 4) chronic tophaceous gout.
Radiologic stages of joint damages	I — large cysts (tophi) in subchondral bone and in deeper layers, soft tissues sealing (sometimes); II — large cysts around joints and minor erosion of the articular surfaces, permanent periarticular soft tissues sealing, sometimes with calcifications; III — large erosion (at least 1/3 of articular surface), osteolysis of epiphysis, significant soft tissues compression with calcium deposits.
Level of functional impairment	0 — retained; I — professional capacity is preserved; II — patients loose professional capacity; III — inability to take care of oneself.
Nephrolithiasis; gouty nephropathy	

Clinical classification of gout is presented in Table 1 [4].

Clinical features. *Acute attack* of gout usually develops after sustained and long-term HU and associated with triggering factors: excessive alcohol intake, prolonged fasting, increased amount of purines in food, injury, exacerbation of co-morbidities, local inflammation (reactive synovitis in osteoarthritis), surgical procedures, use of drugs, etc.

Typical acute attack is observed in 50-80% of cases. Often it occurs suddenly at night. The attack begins with the appearance of sharp pain in the 1st metatarsophalangeal joint (in 60-75%); the joint quickly swells, the skin over it is red, then becomes bluish-red, hot, body temperature increases up to 38-39 °C, skin over the joint glitters and is tense; function of the joint is impaired, resulting in the patient's inability to move (Fig. 1). The first attacks of gout usually last from 3 to 10 days then pain and swelling disappear, skin becomes normal, joint function complete resolution is observed. In some cases, the first signs of disease are damage of joints (metatarsal, ankle, knee, wrist, rarely — small joints of the hand) [2, 6, 16, 24, 40].

The first acute attack usually marks the onset of intermittent gout. In a lot of patients at early stage of disease attacks occur rarely — once every 1-2 years. Later they gradually become more frequent, long-



Fig. 1. Acute gouty arthritis of the 1st metatarsophalangeal joint

term and less sharp, and the intervals between them become shorter and stop to be asymptomatic, indicating that the intermittent gout becomes chronic one.

Chronic gout develops in 5-10 years after the first attack and is characterized by chronic inflammation of the joints and periarticular tissues, appearance of tophi and combination of joint damages, lesions of periarticular tissues and internal organs (mostly kidneys). Renal involvement in patients with gout is not only complication, but also a visceral manifestation of the disease, it is called gouty kidney. Renal lesions can manifest in the form of urolithiasis, interstitial nephritis, glomerulonephritis and arteriolar nephrosclerosis [5, 7, 16, 24, 45].

In patients with chronic gout tophi can be found in multiple locations such as ears (Fig. 2), joints of hands (Fig. 3), feet, ankle, knee, elbow (Fig. 4); less frequently — shoulder, hip, sternoclavicular joints.



Fig. 2. Gouty tophi on the ear



Fig. 3. MSU crystals deposition in the small joints of hand



Fig. 4. MSU crystals deposition near the elbow

Tophi clinical recognition signs are:

- nodular formation, clear boarded from the surrounding tissue and tighter than other tissues;
- cartilaginous, occasionally petrous consistency of formation;
- its surface is granular and rough;
- whitish-yellow colour;
- local tissue swelling which produces brittle-liquid, liquid or pasty substance mass through superficial ulcers.

The main clinical features of secondary gout are:

- frequent and early formation of tophi;
- attacks of significant duration;
- disease frequent development and early onset;
- serum UA high levels [7].

There are 3 degrees of gout clinical course severity (Table 2).

Diagnosis. Laboratory tests. Evaluation of UA metabolism (UA presence in synovial fluid (SF), tophi, blood serum and daily amount of urine; UA clearance determination) and gouty inflammatory process activity degree are very important in diagnosis of gout. During the gouty attack in blood test leukocytosis, C-reactive protein increased level are determined, erythrocyte sedimentation rate (ESR) is gradually increasing; other indicators of acute phase of inflammation are also present. In the study of UA excretion the level of daily uraturia is determined (patient sticks to the 3-day diet that excludes purines (meat, broth, poultry, fish, beans, alcohol)). A high concentrations of urates in daily urine is observed in case of UA excessive formation; renal HU is characterized by a low daily uraturia. In case of kidneys involvement in the pathological process urinary syndrome is possible. In SF high cytosis, reduction of its viscosity, needle-like crystals of MSU are present [2, 3, 6, 36, 41].

Dystrophic and necrotic tissue changes, whitish mass crystals of urates and signs of inflammatory reaction around them are detected with the help of **biopsy** of subcutaneous tophi and subsequent **microscopy**.

X-ray signs of bone-cartilage destruction in gout are narrowing of the joint space, «punches» and erosion of the articular surfaces that, therefore, arise in the case of «germination» of tophi in



Fig. 5. X-ray. Urate infiltration of tissues around the 1st right metatarsophalangeal joint, osteoporosis of the 1st left metatarsophalangeal joint, formation of cysts

bone or articular cavity. Secondary osteoarthritis development is accompanied by subchondral osteosclerosis and osteophytosis.

Ultrasound (US) can detect tophi and «double-contour sign» — extra light line parallel to the line of subchondral bone transition in the cartilage [14, 48, 51].

Magnetic resonance imaging (MRI) can determine tophi in the joint of patients with absence of the usual subcutaneous tophi. This technique is also informative during differential diagnosis of tophi and tumors, infectious processes, tunnel syndromes. In addition, MRI can be a good tool for monitoring of the effectiveness of urate-lowering therapy (ULT).

Computed tomography (CT) can detect tophi, localized intraosseous as well as in the area of tendons and soft tissues. CT (compared with US and MRI) can more accurately differentiate gouty tophi [1, 17, 22, 31, 32].

In 2006 EULAR Standing Committee for International Clinical Studies Including Therapeutics developed 10 recommendations for the diagnosis of gout [19]:

1. In acute attacks the rapid development of severe pain, swelling, and tenderness that reaches its maximum within just 6-12 hours, especially with overlying erythema, is highly suggestive of crystal inflammation though not specific for gout.
2. For typical presentations of gout (such as recurrent podagra with HU) a clinical diagnosis alone is reasonably accurate but not definitive without crystal confirmation.
3. Demonstration of MSU crystals in SF or tophus aspirates permits a definitive diagnosis of gout.
4. A routine search for MSU crystals is recommended in all SF samples obtained from undiagnosed inflamed joints.

Table 2. Degrees of gout clinical course severity

Clinical course severity	Clinical manifestations
Mild	Not more than 1-2 attacks of arthritis occur annually, not more than 2 joints are involved, without X-ray signs of joint destruction, tophi are sporadic.
Moderate	4-5 attacks per year, 2-4 joints are involved, moderate bone-joint destruction, multiple tophi and nephrolithiasis.
Severe	At least 5 attacks of arthritis occur per year, polyarthritis with severe bone-joint destruction is typical, multiple tophi and severe nephropathy.

5. Identification of MSU crystals from asymptomatic joints may allow definite diagnosis in intercritical periods.
6. Gout and sepsis may coexist, so when septic arthritis is suspected Gram stain and culture of SF should still be performed even if MSU crystals are identified.
7. Serum UA levels do not confirm or exclude gout, because a lot of people with HU do not develop gout, and during acute attacks serum levels may be normal.
8. Renal UA excretion should be determined in selected gout patients, especially those with a family history of young onset of gout, onset of gout under age 25, or with renal calculi.
9. X-ray is useful for differential diagnosis and show typical features in chronic gout, but it is not useful in confirming the diagnosis of early or acute gout.
10. Risk factors for gout and associated co-morbidity (obesity, hyperglycaemia, hyperlipidaemia, hypertension, etc.) should be assessed.

Criteria. For a long period of time for the diagnosis of gout **1977 American Rheumatism Association preliminary criteria [37]** were used:

Gout may be diagnosed if 1 of the following criteria is present:

1. MSU crystals in SF.
2. Tophi confirmed with crystal examination.
3. At least 6 of the following findings:
 - asymmetric swelling within a joint on a X-ray;
 - 1st metatarsophalangeal joint is tender or swollen (i.e., podagra);
 - HU;
 - maximal inflammation developed within 1 day;
 - monoarthritis attack;
 - more than 1 acute arthritis attack;
 - redness observed over joints;
 - subcortical cysts without erosions on a radiograph;
 - suspected tophi;
 - SF culture negative for organisms during an acute attack;
 - unilateral 1st metatarsophalangeal joint attack;
 - unilateral tarsal joint attack.

In 2015 an international group of investigators, supported by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), developed new **classification criteria for gout** (Table 3) [8]. These criteria represent an advance over previous ones, with improved performance characteristics and incorporation of newer imaging modalities.

The **differential diagnosis** for goat includes a wide variety of disorders, such as the following:

- acute infectious arthritis (in case of monoarthritis),
- polyarthritis — rheumatoid arthritis, rheumatic and reactive arthritis (in case of polyarthritis),
- osteoarthritis (in case of chronic course).

Table 3. 2015 ACR/EULAR gout classification criteria [8]

Steps	Categories	Score
Step 1. Entry criterion	At least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa	
Step 2. Sufficient criterion (if met, can classify as gout without applying criteria below)	Presence of MSU crystals in a symptomatic joint or bursa (i.e., in SF) or tophus	
Step 3. Criteria (to be used if sufficient criterion not met)		
Clinical		
Pattern of joint/bursa involvement during symptomatic episode(s) ever	Ankle or midfoot (as part of monoarticular or oligoarticular episode without involvement of the 1 st metatarsophalangeal joint)	1
	Involvement of the 1 st metatarsophalangeal joint (as part of monoarticular or oligoarticular episode)	2
Characteristics of symptomatic episode(s) ever: 1) erythema overlying affected joint (patient-reported or physician-observed); 2) can't bear touch or pressure to affected joint; 3) great difficulty with walking or inability to use affected joint.	1 characteristic	1
	2 characteristics	2
	3 characteristics	3
Time course of episode(s) ever. Presence (ever) of ≥ 2 , irrespective of antiinflammatory treatment: 1) time to maximal pain <24 hours; 2) resolution of symptoms in ≤ 14 days; 3) complete resolution (to baseline level) between symptomatic episodes.	1 typical episode	1
	Recurrent typical episodes	2
Clinical evidence of tophus. Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g., Achilles)	Present	4
Laboratory		
Serum UA: Measured by uricase method. Ideally should be scored at a time when the patient was not receiving ULT and it was >4 weeks from the start of an episode (i.e., during intercritical period); if practicable, retest under those conditions. The highest value irrespective of timing should be scored.	<4 mg/dl (<0.24 mmol/l)	-4
	6-8 mg/dl (0.36-0.48 mmol/l)	2
	8-<10 mg/dl (0.48-<0.60 mmol/l)	3
	≥ 10 mg/dl (≥ 0.60 mmol/l)	4
SF analysis of a symptomatic (ever) joint or bursa (should be assessed by a trained observer)	MSU negative	-2
Imaging		
Imaging evidence of urate deposition in symptomatic (ever) joint or bursa: US evidence of double-contour sign or DECT demonstrating urate deposition	Present (either modality)	4
Imaging evidence of gout-related joint damage: conventional radiography of the hands and/or feet demonstrates at least 1 erosion	Present	4

Note. Score of ≥ 8 classifies an individual as having gout.

For the differential diagnosis between acute gout and **acute infectious arthritis** it is necessary to collect anamnesis: gout is characterized by recurrent pain attacks, often caused by eating purine rich foods, excessive alcohol intake, etc., without residual effects, acute infectious arthritis is characterized by infection or trauma presence, arthritis prolonged duration, lymphangitis, efficacy of antibiotics.

Rheumatic fever occurs mostly in children and adolescents; it has migratory clinical course, often accompanied by carditis and high titers of antistreptococcal antibodies, that is not typical for gout.

Rheumatoid arthritis (RA) is characterized by:

- gradual onset, without acute crisis;
- first manifestations of RA are symmetric lesions of joints of hand (metatarsophalangeal joint of big toe is affected rarely);
- lack of hyperaemia of the skin over the joint;
- morning stiffness;
- rapid development of muscle atrophy;
- stable high levels of ESR, often rheumatoid factor is detected;
- over few months from the onset of the disease typical radiologic signs of RA can be detected (in case of gout — after 4-5 years).

Radiographically RA is characterized by systemic osteoporosis, and in case of gouty arthritis osteoporosis is local. Systemic osteoporosis can be detected in case of combination of gout with **osteoarthritis (OA)**.

Typical for OA Heberden's nodules are sometimes considered as gouty tophi, but in OA nodules are found in the area of distal interphalangeal joints of the fingers, where tophi usually are not localized. Nodules, unlike tophi have solid consistency. Moreover, in OA primarily the large joints are affected: hip, knee, joints, spine joints, whereas in case of gout — metatarsophalangeal and talocrural ones [2, 5-7].

The goals of gout **treatment** are the elimination of acute attacks of arthritis and inflammatory changes in the joints, reducing the level of serum UA, elimination of extra-articular lesions associated with gout, musculoskeletal system function resolution [10, 17, 26, 28, 33, 47].

General principles of gout management (EULAR, 2006) [20]:

- Optimal treatment of gout requires both non-pharmacological and pharmacological modalities and should be tailored according to:
 - specific risk factors (levels of serum UA, previous attacks, radiographic signs);
 - clinical phase (acute/recurrent gout, intercritical gout, and chronic tophaceous gout);
 - general risk factors (age, sex, obesity, alcohol consumption, urate raising drugs, drug interactions, and comorbidity).

- Patient education and appropriate lifestyle advice regarding weight loss if obese, diet, and reduced alcohol (especially beer) are core aspects of management.
- Associated comorbidity and risk factors such as hyperlipidaemia, hypertension, hyperglycaemia, obesity, and smoking should be addressed as an important part of the management of gout.

Diet in gout should be well-balanced and contain the proper amount of selected nutrients, not only low-purine but also alkalizing products, rich in antioxidants, and provide an adequate amount of fluids [25].

Meat and fish are excluded from meals for the entire exacerbation period. Low-purine diet prevalently consists of liquid food (milk products, rose-hip infusion, vegetable soups, liquid porridges), tea with milk or lemon, decoction of wheat bran with sugar or honey. It is important to exclude purine rich products (liver, kidneys, brain, meat and meat soups, cocoa, chocolate), stop to drink alcohol and sugar-sweetened soda. It is preferred to include alkaline mineral water. It is also necessary to increase cherry consumption or vitamins B₁ and C intake. This diet will contribute to the normalization of purine metabolism and reduce increased UA synthesis [6, 25, 27].

Pharmacological treatment. In 2014 Broad panel of rheumatologists in the 3e (Evidence, Expertise, Exchange) Initiative developed the multinational evidence-based recommendations on the management of gout [35]:

1. Acute gout should be treated with low-dose colchicine (up to 2 mg daily), NSAIDs and/or glucocorticoids (intra-articular, oral or intramuscular) depending on comorbidities and risk of adverse effects [18, 42, 50].
2. Allopurinol is the 1st line ULT; alternatives to consider next include uricosurics (eg, benzbromarone, probenecid) or febuxostat; uricase as monotherapy should only be considered in patients with severe gout in whom all other forms of therapy have failed or are contraindicated (Table 4). ULT (except uricase) should be started in a low dose and escalated to achieve a target serum UA [26, 39, 41, 46, 49].
3. When introducing ULT, patient education on the risk and management of flare is essential [38]; prophylaxis should be considered using colchicine (up to 1.2 mg daily), or if contraindicated or not tolerated NSAIDs or low dose glucocorticoids may be used. The duration of prophylaxis is individual.
4. In patients with mild-moderate renal impairment, allopurinol may be used with close monitoring for adverse events, starting at a low daily dose (50-100 mg) up-titrated to achieve usual

- target of serum UA; febuxostat and benzbromarone are alternative drugs that can be used without dose adjustment [39].
- The treatment target is serum UA below 0,36 mmol/l, and the eventual absence of gout attacks and resolution of tophi; monitoring should include serum UA level, frequency of gout attacks and tophi size [26, 33].
 - Tophi should be treated medically by achieving a sustained reduction in serum UA, preferably below 0.30 mmol/l; surgical treatment is only indicated in selected cases: nerve compression, mechanical impingement or infection.

Table 4. Currently available ULT in the management of gout [41, 46]

Drug	Dose	Route/Schedule
Xanthine Oxidase Inhibitors		
Allopurinol	50-800 mg	Orally daily
Febuxostat	40-120 mg	Orally daily
Uricosurics		
Probenecid	500-2000 mg	Orally twice daily
Sulfinpyrazone	200-800 mg	Orally twice daily
Benzbromarone	50-200 mg	Orally daily
Uricases		
Pegloticase	8 mg	IV every 2 weeks

- Pharmacological treatment of asymptomatic HU is not recommended to prevent gouty arthritis, renal disease or cardiovascular events [35, 36].

Prevention. The aim of **primary prophylaxis** is examination of patient's family for latent HU excluding, in case of its presence alcohol intake, consumption of fatty and protein foods should be reduced, physical exercises and sport are recommended.

Secondary prophylaxis. Patients with HU and gout are in need of constant supervision in outpatient setting. In case of disease mild course the examination of internist and rheumatologist, blood and urine tests should be performed twice a year. In case of moderate and severe course of gout previously named tests should be carried out once per 3 months. X-ray of joints and US of kidneys should be performed annually [2, 3, 7].

Prognosis is defined by renal and cardiovascular system involvement. Unfavorable prognostic factors are:

- onset of gout under the age of 30 years;
- severe HU (above 0.6 mmol/l) and hyperuraturia (more than 1100 mg/day);
- nephrolithiasis with urinary infections;
- diabetes mellitus;
- hypertension.

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ПОДАГРА: СУЧАСНІ ПОГЛЯДИ НА ДІАГНОСТИКУ ТА ЛІКУВАННЯ

А.С. Свінцицький

Резюме

У статті наведено сучасні погляди на питання діагностики, лікування і профілактики подагри, які базуються на положеннях останніх українських і міжнародних клінічних настанов.

Ключові слова: подагра, гіперурикемія, сечова кислота, класифікаційні критерії, діагностика, лікування, профілактика.