BULGARIAN SOCIETY OF RHEUMATOLOGY

CONSENSUS

DIAGNOSIS AND TREATMENT OF GOUT

Rada Gancheva, MD, PhD

Pavlina Pavlova, MD

Prof. Zlatimir Kolarov, DMedSc

March, 2019

INTRODUCTION

Gout is a metabolic inflammatory joint disease characterized by the accumulation of monosodium urate (MNU) crystals in the joints and surrounding joints, at serum uric acid (PC) levels exceeding the physiological solubility threshold.

It is part of the group of crystalline arthropathies (associated with the accumulation of: calcium pyrophosphate dihydrate; basic calcium phosphate (apatite); calcium oxalate) and is associated on the one hand with hyperproduction or decreased excretion and on the other with the metabolic syndrome. The development of gout is also associated with genetic factors. In Bulgaria, about 10% of the population has a genetically determined increased serum PC, without leading to an increased incidence of gout.

The incidence of the disease has been gradually increasing over the last few decades. It mainly affects men, with a male to female ratio of 9:1. Menopause increases the risk of developing gout in women. According to recent studies, the incidence in the United States is 3.9% of the adult population, which is about 8.3 million people, in the UK – 1.4% of the population, and with age it reaches 7% in men over 75 years. age. In some ethnic groups, such as the Maori in New Zealand, the incidence varies from 6.1% in the general population to 70% in men over the age of 75.

This is due to the increased incidence of diseases associated with the occurrence of hyperuricemia – hypertension, obesity, metabolic syndrome, type 2 diabetes (DT2) and chronic renal failure (CRF). Other factors include dietary habits, excessive alcohol consumption, and the increasing use of thiazide

and loop diuretics in patients with cardiovascular disease. In recent years, hyperuricemia has been shown to be an independent risk factor for hypertension and chronic renal impairment. It also plays a role in some of the characteristics of the metabolic syndrome, including hepatic steatosis and insulin resistance. Secondary hyperuricemia and gout also occur in myelo and lymphoproliferative diseases, especially during their treatment.

Despite its widespread prevalence, gout is often not properly diagnosed or diagnosed late, and even when detected in time, treatment is not always optimal. Continued urate deposition not only provokes new joint crises, but can also lead to chronicity of the process with subsequent irreversible joint damage and disability.

Urate deposition in the kidney is often not reported clinically due to lack of complaints and pain, but leads to renal failure and death.

THE STRATEGY FOR BEHAVIOR IN GOUT

Diagnosis

The gold standard for diagnosing gout is the isolation of MNU crystals from joint fluid or tissue biopsy. This should be a routine procedure, as it is usually followed by lifelong urate-lowering therapy (ULT).

Some elements of the medical history combined with physical examination data may be considered in the diagnosis – sudden onset of complaints, swelling and redness involving the first metatarsophalangeal or tarsal joint, together with a history of previous similar complaints. It is known that such a characteristic

of self-limiting synovitis with erythema also occurs in other crystalline synovitis (e.g., calcium pyrophosphate dihydrate-associated synovitis or so-called pseudogout), septic or reactive arthritis. The involvement of the first metatarsophalangeal joint and the establishment of tophi on physical examination makes the diagnosis even more certain. But the involvement of the first metatarsophalangeal joint with edema and inflammation occurs in up to 20-25% of crises and for this it is necessary to look for defeat of any joint.

Laboratory tests

Hyperuricemia is a major risk factor for developing gout. Epidemiological studies have shown that people with persistent hyperuricaemia above 9 mg/dl have a 20% risk of developing gout.

Changes in the external conditions of the environment change the solubility of the ions accumulated in a higher concentration. This leads to crystal formation and joint crisis. Changes leading to acidosis are:

- tight shoes
- mechanical load – prolonged walking and fatigue
- dietary errors
- starvation, rapid weight loss
- thirst
- fever

Without acidosis on the spot, there is no crisis.

People with high levels of UA often have concomitant pathology – metabolic syndrome, diabetes, cardiovascular or renal pathology. The high percentage of hyperuricemia in the general population determines its role in the diagnosis of gout as supportive rather than determining. In general, each laboratory calculates its own threshold for hyperuricaemia, which is two standard deviations above the mean for a given healthy population. The fact that the normal value of UA in men is higher than in women is also taken into account. Different reference limits for a given population also determine different degrees of importance of hyperuricemia as a diagnostic criterion. Serum UA levels should not be used to diagnose or rule out a diagnosis, either during a joint crisis or in the interictal period.

The increase in acute phase parameters is a consequence of the activation of the NLRP3 inflammasome, which leads to the IL-1-mediated induction of CRP and IL-6. These tests are not specific and are not used to diagnose gout.

The study of renal function and in particular the urate excretion/creatinine excretion ratio is useful

for proving cases of uric acid overexcretion, and assists in the choice of treatment. It is not specific for diagnosis, but is a guide for determining the genesis of hyperuricemia. It is done by collecting 24-hour urine for testing. For overexcretion, ≥ 1000 mg/24 h is considered, and for insufficient < 6 ml/min.

Imaging research

Very often crystalline arthropathy is mixed (urate + calcium pyrophosphate + calcium apatite). Therefore, the role of conventional radiography in the diagnosis of gout is important, even more so radiographic changes (erosive arthropathy without periarticular osteopenia, with erosive or sclerotic borders, soft tissue shadows and marginal osteophytes) occur in the years 5 years after the onset of the disease. has passed to its chronic phase with or without the formation of tophi. Subcutaneous tophi can be detected on physical examination. In the last few years, new imaging methods have been introduced to visualize asymptomatic MNU deposits. This can be considered as an indication for initiating urate-lowering therapy.

The “double loop” of the joint ultrasound and the double-energy computed tomography (DECT) MNU deposits are included in the classification criteria of the American College of Rheumatology (ACR) from 2015.

Classification criteria

Several classifications are used to diagnose gout. The most commonly used criteria are ACR from 1977. They diagnose acute arthritis, and in the interictal period of the disease may be unfeasible. The gold standard for diagnosis is the identification of MNU crystals in the synovial fluid. In clinical practice, it is necessary to diagnose the disease accurately without identifying the crystals, as most patients are treated in outpatient care, where synovial fluid is not routinely examined. In 2015, the ACR and the European League Against Rheumatism (EULAR) introduced new classification criteria (Table 1 and Table 2).

Experts take into account the fact that during the examination there may be a false-positive „double contour“ of the joint surface, but it disappears with the change of the angle of insonation. DECT images should be obtained with an 80 kV and 140 kHz scanner using a gout-specific program that encodes MNU deposits in color. A positive result is the presence of color-coded urate deposits intra-articularly and peristally. The new criteria are only applicable to individuals with symptoms of the disease. The prognosis of

patients with asymptomatic disease is not well described. Inclusion criteria are at least one episode of swelling and pain in a peripheral joint or bursa. A sufficient criterion is the detection of MNU crystals in the symptomatic joint or bursa, or the presence of tophi. Experts have judged that there should be no exclusionary indicators, because gout is often combined with other diseases, and microscopy of synovial fluid does not always show crystals in patients with gout. Synovial fluid for analysis needs to be aspirated from a joint or bursa that has been inflamed at least once. There is a lack of literature data and clinical experience to support the diagnostic ability of MRI and CT.

At a serum uric acid level of $4 - < 6$ mg/dl ($240 - < 360$ μ mol/l), the score is 0. If synovial fluid is not assessed, the score for this criterion is 0. If no imaging study has been performed, the score at these points is also 0. A web calculator is available at <http://goutclassificationcalculator.auckland.ac.nz>, and on the ACR and EULAR websites. The maximum number of points is 23. A value ≥ 8 classifies the individual as having gout. These classification criteria have better characteristics than the previous ones and allow the diagnosis to be made on the basis of clinical data (Table 3).

Table 1. Characteristics of the criteria included in the new classification

	Characteristics
1. Acute inflammation involving the joint or bursa.	Joints and bursae other than the ankle, tarsus or first metatarsophalangeal joint (or their involvement is part of polyarticular involvement). Monoarticular involvement of the ankle or tarsus or part of an oligoarticular involvement without the first metatarsophalangeal joint. The first metatarsophalangeal joint, such as monoarticular or oligoarticular involvement.
2. Characteristics of inflammatory episodes.	Difficulty walking or inability to use the affected joint (described by patients). Inability to tolerate touch or pressure on the affected joint (described by patients). Erythema of the affected joint.
3. Duration of acute inflammation.	Typical gout attack – the presence of more than 2 of the following characteristics, regardless of anti-inflammatory treatment: Maximum pain development time < 24 h. Relief of symptoms for ≤ 14 days. Complete switching of symptoms between episodes of acute inflammation.
4. Clinical tophi	Localized in the joints, on the olecranon, the pads of the fingers, the tendons.
5. Serum uric acid level without treatment: < 4 mg/dl (0.24 mmol/l) $4 - < 6$ mg/dl ($0.24 - < 0.360$ mmol/l) $6-8$ mg/dl ($0.36 - < 0.48$ mmol/l) $8 - < 10$ mg/dl ($0.48 - < 0.60$ mmol/l) ≥ 10 mg/dl (≥ 0.60 mmol/l)	The highest measured serum uric acid level without urate-lowering therapy is reported. Serum levels should be measured when the patient is not receiving urate-lowering therapy or more than 4 weeks have passed since the onset of acute inflammatory arthritis. If the serum uric acid level is > 10 mg/dl, no re-examination is required.
Analysis of synovial fluid.	Localization: inflamed joint or bursa. The presence of MNU crystals is a sufficient criterion.
MNU deposits proven by imaging studies.	Ultrasonography or DECT “Double loop” or urate deposits evidenced by DECT in a symptomatic joint or bursa.
Gout-related joint damage, proven by imaging.	X-ray – the presence of erosion characteristic of gout; disturbance of the corticalis with sclerotic border and overhanging edge, the distal interphalangeal joints of the hands and feet are excluded from the analysis.

Table 2. ACR/EULAR classification criteria for gout

Step 1. Inclusion criteria (the following criteria apply only to patients who meet the inclusion criteria)	At least one episode of swelling, pain and tenderness in a peripheral joint or bursa.	
Step 2. Sufficient criterion, if met, the diagnosis can be made without taking into account the other criteria.	Presence of MNU crystals from inflamed joint or bursa or isolated from tofa.	
Step 3. Criteria to be used if the sufficient criterion is not met:	Engagement of the ankle or tarsus as part of monoarthritis or oligoarthritis without affecting the first metatarsophalangeal joint.	1
Clinical – a pattern of involvement of a joint or bursa during an acute episode.	Involvement of the first metatarsophalangeal joint as part of monoarthritis or oligoarthritis.	2
Characteristics of the inflammatory episode		
• Erythema of the affected joint.	One characteristics	1
• Intolerance of touch or pressure on the affected joint.	Two characteristics	2
• Difficulty walking and inability to use the joint.	Three characteristics	3
Duration of the acute inflammatory episode		
Presence of ≥ 2 , regardless of anti-inflammatory treatment:	A typical crisis	1
Time for development of maximum pain < 24 h.	Recurring crises	2
Relief of symptoms for ≤ 14 days.		
Complete recovery between episodes of acute inflammation.		
Clinical tophi in the joints, olecranon, finger pads and tendons.	Present	4
Laboratory		
Serum uric acid level determined by uricase method.	< 4 mg/dl (0.24 mmol/l)	-4
It is appropriate to determine when the patient is not receiving urate-lowering treatment or more than 4 weeks have passed since the onset of acute inflammation (during the interictal period). The highest measured value is reported.	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 ($\geq$ 0.60 mmol/l)	4
Analysis of synovial fluid from an inflamed joint or bursa.	Negative for MNU crystals	-2
Image methods		
Proof of the presence of MNU crystals in the joint or bursa.	Present	4
„Double contour“ from ultrasonography or MNU deposits from DECT.	Present	4
At least one radiographic erosion.		

Table 3. Sensitivity and specificity of the existing classification criteria

Criteria	AUC	Sensitivity	Specificity
ACR/EULAR criteria	0.95	0.92	0.89
ACR/EULAR (only clinical criteria)	0.89	0.85	0.78
ACR 1977	0.83	1.00	0.51
Rome	0.95	0.97	0.78
Rome (only clinical criteria)	not applicable	0.77	0.78
New York	0.83	1.00	0.78
New York (only clinical criteria)	not applicable	0.79	0.78
Mexico	0.84	1.00	0.44
Mexico(only clinical criteria)	not applicable	0.95	0.44
Netherlands	0.87	0.95	0.59

Stages of the disease

In addition to the need for new classification criteria, it is considered that a new staging of the disease is needed. In 2014, N. Dalbeth and L. Stamp summarized that the clinical staging of gout presents its symptomatology, but does not reflect major pathogenetic aspects. They offer new staging:

Stage A. Hyperuricemia, but without MNU deposits or symptoms of gout.

Stage B. Presence of MNU crystals, proven by microscopy or additional imaging, but without symptoms of gout.

Stage C. Available MNU crystals with anamnestic or current symptoms of acute gout crisis.

Stage D. Advanced gout, requiring complex care.

This staging indicates that the disease is due to the deposition of crystals and allows in the absence of symptoms to be screened and treated. In asymptomatic patients, crystalline deposits cause structural damage. It is not yet clear whether initiating urate-lowering treatment in them reduces cardiovascular risk and stops structural joint damage.

Hyperuricemia and metabolic disorders

Most patients with asymptomatic hyperuricemia never develop gout or kidney stones. But patients with hyperuricemia are characterized by metabolic disorders. In patients with metabolic syndrome, the mean serum uric acid level is higher than in controls. The mean serum uric acid level was found to correlate with the incidence of metabolic syndrome. The NHANES III analysis reported a higher incidence of metabolic syndrome in patients with hyperuricaemia than in patients with normouricaemia. Hyperuricemia is a predictor of fatty liver development, obesity, hypertension and high CRP. The relationship between hyperuricaemia and metabolic syndrome does not depend on renal function. The reason for this fact has not yet been established. One of the intersections between uric acid and metabolic syndrome is fructose. Uncontrolled fructose metabolism causes increased intracellular ATP breakdown, increased uric acid synthesis, endothelial dysfunction, oxidative stress and increased lipogenesis. Serum uric acid rises from 30 to 60 minutes after fructose intake and its 24-hour levels remain high. Increased fructose intake causes insulin resistance and other manifestations of the metabolic syndrome. Studies in rats have shown that treatment with allopurinol improves blood pressure, insulin resistance, hyperglycaemia and hypertriglyceridaemia. Hyperuricemia has been shown to stimulate fat accumulation in the liver by inducing mitochondrial oxidative stress. The link between uric acid, metabolic syndrome and type 2 diabetes is insulin resistance.

The relationship between serum uric acid levels and insulin resistance has been demonstrated in patients with normal fasting blood sugar and normal glucose tolerance. Hyperuricaemia may precede hyperinsulinemia, obesity and diabetes. Uric acid stimulates intracellular oxidative stress and impairs endothelial function. It has a direct pro-inflammatory and prooxidative effect on adipocytes. These properties are the basis of insulin resistance. There is a hypothesis that links hyperuricemia, decreased urinary uric acid excretion and insulin resistance. According to her, hyperuricemia is the „peak“ of the multime-

tabolite syndrome, in which insulin-mediated renal hemodynamic disorders lead to kidney damage from hypertension. K. Ogino demonstrated that in patients with congestive heart failure, lowering serum uric acid with benzbromarone improves insulin resistance. Another study reported that lowering serum uric acid normalized HbA1C% in diabetics with normal blood pressure. In turn, hyperinsulinemia increases the re-absorption of uric acid in the proximal tubule.

Insulin reduces the renal excretion of sodium, chlorine and uric acid. These effects of insulin are not altered in patients with insulin resistance and hypertension.

There are currently no randomized trials to determine whether treatment of asymptomatic hyperuricaemia slows the development and progression of metabolic syndrome, type 2 diabetes and renal failure. Its pharmacological treatment carries some risk. It is not considered useful and justifiable for its price and is generally not recommended. Patients with asymptomatic hyperuricaemia require lifestyle changes, diet, reduced alcohol intake and exercise to lower serum uric acid levels. Exceptions are patients with cancer who are on cytolytic treatment. They should carry out prophylaxis against acute urate nephropathy. Over the years, attempts to prevent urate nephropathy, especially in oncological conditions, have led to a reduction in mortality.

Intravenous infusion of saline, furosemide and mannitol is necessary to prevent further precipitation of uric acid. Alkalization of urine with sodium bicarbonate or acetazolamide enhances the elimination of uric acid. Razburicase (Elitek) is a recombinant urate oxidase approved for the treatment of tumor lysis syndrome in both adults and children. Facilitates the conversion of urate into the more soluble product allantoin. Although treatment with Razburicase is standard in the care of patients at high risk of tumor lysis syndrome, there is debate as to whether a rapid decrease in serum uric acid levels has a beneficial effect on the prognosis of patients. In patients with leukemia and lymphoma, doses of the order of 600-900 mg/24 h are given before chemotherapy to reduce uric acid production. Early hemodialysis begins with the development of acute renal failure in order to reduce whole body urate load and facilitate the restoration of renal function.

BASIC RECOMMENDATIONS FOR PATIENTS DIAGNOSED WITH GOUT

The recommendations prepared by the American College of Rheumatology (ACR) were published

in October 2012 in the journal *Arthritis Care and Research*. Later, in 2016, EULAR developed three basic and 11 key recommendations. All of them are in line with the importance of risk factors for patients with gout and the emergence of new, approved urate-lowering drugs – febuxostat, pegloticase, IL-1 blockers, Lesinurad. The recommendations emphasize the safety and quality of therapy and are in line with good clinical practice. They do not replace the individualized approach in each patient in combination with the clinical thinking of the competent specialist. They are aimed primarily at reducing serum PC levels. The aim is to reduce the risk of gout crises and their frequency. The emphasis is on dietary и поведенчески мерки за поддържане на идеално здраве.

Patient education with initiation of diet and lifestyle changes (Table 4).

According to the latest EULAR recommendations from 2016, every patient with gout should be informed about the pathophysiology of the disease, the availability of effective treatment, the concomitant pathology and the principles of treatment of acute crisis, and the clearance of urate accumulations by lifelong maintenance of low uric acid levels. There is talk of „treatment to reach the target urate level“, effective for controlling all the features of the disease. According to ACR 2012, foods are grouped into three categories called „avoid“, „reduce“ and „consume more“. It is rec-

ommended to reduce the intake of purine-rich meats and seafood, as well as to sweetened with corn syrup, fructose-rich soft and energy drinks (Level C) and to encourage the intake of low-fat and skimmed dairy products. Vegetable intake is encouraged, taking into account the evidence in healthy subjects for a reduction in serum UA and urinary urolithiasis risk factors in relation to vegetable intake. Reduced alcohol consumption is recommended (especially beer, but also for wine and concentrated alcohol) and abstinence from alcohol abuse in all patients with gout (Level B). In addition, complete abstinence from alcohol is recommended during periods of active arthritis, especially in inadequate medical control of the disease and chronic gouty arthropathy with tophi.

Changes in diet and lifestyle alone provide a therapeutically insufficient reduction in serum PC and/or prevention of gout crises in a large proportion of individuals with gout. Clinical studies related to diet and physical activity have shown only about a 10-18% reduction in serum PC.

Look for causes of secondary hyperuricemia (concomitant pathological conditions) (Table 5)

Assessment of the possibility of discontinuation of drugs that are not essential for the treatment of concomitant diseases niacin for the treatment of hyperlipidemia:

– thiazide and loop diuretics for hypertension (although, in a discussion format and without an explicit opinion, the working group emphasizes the impor-

Table 4. Specific recommendations regarding health, diet and lifestyle changes in patients with gout

Weight loss in obese patients to reach a healthy BMI		
Overall healthy diet *		
Excercises (achieving good physical condition)		
Smoking cessation		
Sufficient level of hydration		
To avoid	To reduce	Consume more*
Organic meats, rich in purines (ex. Liver, kidneys)	Portions of: : Beef, Lamb, Pork Sea food, rich in purines (ex. Sardines, oysters). Portions of natural, but sweet	Low fat or non-fat products
Non-alcoholic and ga-drinks or foods sweetened with corn fructose	Fruit juices Table sugar and sweetened drinks and desserts Table salt including in the composition of sauces and dressings.	Vegetables
Alcohol abuse (defined as more than 2 servings a day for men and more than 1 serving a day for women) Any use of alcohol in the periods of frequent attacks of acute gout, arthritis or advanced gout with poor control	Alcohol (especially beer, but also wine and other kinds of alcohol) in all patients with gout	

* The recommendation to „increase consumption“ does not mean encouraging patients to consume excessive amounts of certain foods. No consensus has been reached on the consumption of: cherries and cherry products, ascorbic acid (in food supplements or in the composition of various foods), nuts and legumes. There has been no discussion regarding the consumption of purine-rich vegetables and legumes.

tance of treatment with thiazide diuretics in many patients with hypertension and draws attention to their unwarranted discontinuation due to hyperuricaemia at the cost of poor control of A).;

– calcineurin inhibition with cyclosporine and tacrolimus when not relevant for immunosuppression.

Table 5. Specific recommendations for screening for concomitant diseases in patients with gout

It is appropriate to take them into account in the clinical evaluation and, if there are indications, to specify:
Obesity, dietary factors;
Excessive alcohol use;
Metabolic syndrome, type 2 diabetes;
Hypertension*;
Hyperlipidemia, modifiable risk factors for coronary heart disease and stroke;
Medications, increasing the serum PK*;
History of urolithiasis;
Chronic kidney disease, glomerular or interstitial (eg analgesic nephropathy, polycystic kidney disease);
In some selected cases, potential genetic or acquired causes of PC overproduction (eg congenital defects in purine metabolism, psoriasis, myeloproliferative or lymphoproliferative diseases)
Iron intoxication

* without special voting, the important benefits of thiazide diuretics for blood pressure control and its possible consequences in many patients with hypertension were highlighted.

Effects of some drugs used in cardiology on uric acid levels.

From the group of **ACE inhibitors – captopril and enalapril** increase the excretion of urate through the kidneys. Captopril significantly reduces serum PC levels in patients with hypertension. Diuretics-induced hyperuricaemia can be overcome by co-administration with captopril or enalapril. The Systolic Hypertension in the Elderly (SHEP) study found that patients who maintained good blood pressure control with a thiazide diuretic but at the same time increased serum PC levels did not have a beneficial effect on the cardiovascular system. **Beta-blockers** increase serum UA levels. The effect of **calcium antagonists** on its concentration is controversial. In rats, intravenous administration of diltiazem has a uricosuric effect because it increases the glomerular filtration rate. A. Tykarski et al. found that after ten days of diltiazem administration, serum UA levels, clearance and excretion did not change significantly. On the other hand, the Coronary Disease Trial Investigating Outcome with Nifedipine GITS (ACTION) study reported that nifedipine lowered serum UA levels.

The angiotensin-2 receptor blocker, losartan, increases urinary PC excretion and decreases serum levels in healthy and hypertensive patients. Following administration of 100 mg losartan, the plasma concentration of PC decreased by 8% after 1/2 hours and by 16% after 2 1/2 h. PC excretion increased by 3.9 times in the first to second hour and by 2.6 times in the second to third hour. Losartan has a similar effect to probenecid. Following administration of losartan, renal urate clearance was increased threefold in rats with normo- and hyperuricaemia. An increase in urate clearance of 17 to 25% has been reported in the treatment of hypertensive and renal transplant patients. In hypertensive patients, hyperuricaemia induced by thiazide diuretics is normalized. Uricosuria due to its intake does not lead to changes in the kidneys because it raises the pH of urine. In diabetic nephropathy, the hypouricemic effect of the drug reduces the risk of deterioration of renal function. A decrease in serum PC level of 0.5 mg/dl reduced the risk of deterioration in renal function by 6%. There is evidence that 25% of the renoprotective effects of losartan are due to its hypouricemic properties. On the other hand, the development of acute renal failure after exercise has been reported in a patient with renal hypouricaemia treated with losartan and trichloromethiazide. Renal failure has reversed with the replacement of losartan with candesartan. A biopsy showed that the kidney had recovered from the acute tubular necrosis. It should be noted that losartan, but not other angiotensin-2 receptor blockers, affects renal urate retention. Therefore, it is the drug of choice for controlling blood pressure and lowering serum PC levels in hypertension combined with hyperuricemia or gout. Its uricosuric action is due to the inhibition of URAT1 in the renal proximal tubules. Data from Losartan Intervention For End Point Reduction in Hypertension (LIFE) show that its use in patients with hyperuricaemia reduces the risk of death, myocardial infarction and stroke. Sulfapyrazone in patients with coronary heart disease is associated with a lower risk of myocardial infarction and sudden cardiac death. In patients with unstable angina pectoris, the beneficial effect of sulfapyrazone has not been proven.

Atorvastatin and rosuvastatin lower serum PC levels. Serum levels of PC, endothelin-1 and angiotensin-2 are reduced during treatment with rosuvastatin. In rats with induced hyperuricaemia, its therapeutic effect was better than that of allopurinol. Rosuvastatin may be a new drug for the treatment of hyperuricemia due to its protective effect on the endothelium. There is evidence that fenofibrate low-

ers PC levels by 20%. In patients with dyslipidemia, treatment with 300 mg/24 h. fenofibrate for 12 weeks decreased the serum concentration of PC by 36% and at the same time increased its excretion by 62%. In patients without dyslipidemia, three days of 450 mg fenofibrate decreases the plasma level of PC and increases its fractional excretion. Its mechanism of action is by blocking the renal transporter – URAT1. N. Choi et al. found that people with higher vitamin intake. C have a lower risk of developing gout. A study conducted on healthy volunteers showed that the intake of 500 mg/24 h. vit. C for 2 months lowers serum PC levels. Its mechanism of action is unclear. It is believed that vit. C increases the excretion of PC. The latest study conducted in this direction in patients with gout found that its intake at a dose of 500 mg/24 h. for 8 weeks does not significantly lower the level of UA.

Clinical assessment of the severity of gout – palpable tophi, frequency and severity of acute and chronic signs and symptoms.

It is very important to explain the need for lifelong treatment together with lifestyle advice to patients in order to ensure good compliance and therefore a better prognosis of the disease.

RECOMMENDATIONS FOR CONDUCTING PHARMACOLOGICAL CPT IN PATIENTS DIAGNOSED WITH GOUT.

Indications for CPT.

Gout and:

- One or more tophi found during the clinical examination or imaging examination
 - Frequent attacks of acute gouty arthritis (≥ 2 times a year)
 - Chronic renal failure (CRF) ≥ 2 degree
 - History of urolithiasis
- EULAR – 2016 – Recommendation 5
- age under 40 years.
 - and/or PC ≥ 8 mg/dl (480 μ mol/l)
 - and/or concomitant diseases – AH, CH, IBS, kidney disease

Patients should be informed in detail and actively participate in the choice of CPT.

The goal of treatment is to reach and maintain the target UA level in the individual patient < 6 mg/dl or < 356.88 μ mol/l. In some cases, in order to facilitate the dissolution of the accumulated crystals in the more severe course of the disease (tophi, chronic arthropathy, frequent seizures) it is necessary to lower the UA < 5 mg/dl or < 297 μ mol/l.

Some clinical trials have shown that uric acid can prevent the development of certain neurodegenerative diseases, such as Parkinson's disease, Alzheimer's disease or amyotrophic lateral sclerosis.

Given these data and taking into account the potential for severe reductions in serum uric acid levels with CPT, EULAR does not recommend maintaining values < 3 mg/dl in the long term.

Therapy begins with one of the first-line drugs:

- xanthine oxidase inhibitor (COI) – allopurinol or febuxostat according to ACR, while EULAR recommends allopurinol first and in case of failure of the target values of PC – febuxostat.
- if at least one COI is contraindicated or poorly tolerated, an alternative treatment option is the uricosuric agent probenecid according to ACR or benzbromarone according to the latest EULAR recommendations from 2016.

According to EULAR Recommendation 7 of 2016, CPT should be started at a low dose and titrated until the target levels are reached. UA values < 6 mg/dl should be maintained for life. A clinical trial found that in 40% of successfully treated patients, gout attacks resumed after 5 years of discontinuation of CPT.

Xanthine oxidase inhibitors – uric inhibitors

Key recommendations for allopurinol treatment

The mechanism of action is associated with blocking the enzyme xanthine oxidase, which reduces the conversion of hypoxanthine and xanthine to UA. The plasma concentration of uric acid decreases, but that of its precursors – hypoxanthine and xanthine, which, in contrast, are well soluble and have a much better renal clearance.

Allopurinol is currently the most commonly prescribed drug for reducing serum UA levels.

- The initial dose, with preserved renal function, should not be higher than 100 mg/day, and in patients with CKD $\geq$ grade 4 – no more than 50 mg/day (Level B). Higher starting doses increase the incidence of acute crises and severe skin side effects.
- The maintenance dose should be gradually increased by 100 mg every 2-4 weeks to the appropriate maximum dose required to achieve a specific target UA level. In 30-50% of patients with preserved renal function, the most commonly used dose of 300 mg daily is insufficient to reach the target levels. Treatment with allopurinol at doses of 600-800 mg daily has between 75-80% success in reaching the target UA < 6 mg/dl (360 μ mol/l).

- According to ACR, the dose may be increased above 300 mg/day, even in renal impairment, pro-

vided that this is accompanied by adequate patient training and monitoring for drug toxicity (pruritus, rash, elevated liver transaminases). According to EULAR 2016, recommendation 9 – in renal involvement, the maximum allowable dose of allopurinol should be calculated depending on creatinine clearance. If the target UA is not reached at this dose, the patient should be switched to febuxostat or benzbromarone with/without allopurinol, except in cases of eGFR < 30 ml/min.

- The HLA (human leukocyte antigen) test – B * 5801 in selected patients, especially in subpopulations with a higher risk of severe allopurinol hypersensitivity reactions (eg Koreans with CKD ≥ above grade 4, HanChinese), should be considered prior to initiating therapy and Thai regardless of renal function) (Level A). The incidence of such severe reactions was estimated to be 1: 1000 for the United States. This includes not only Stevens-Johnson syndrome and toxic epidermal necrolysis, but also systemic manifestations such as eosinophilia, vasculitis, skin rash and severe organ failure. The presence of renal involvement and the use of thiazide diuretics have been reported as additional risk factors for the development of severe hypersensitivity reactions to allopurinol.

Although it is the most common drug, hypersensitivity reactions, together with the inability to reach serum PC targets in so-called allopurinol-refractory patients, limit its use.

It should be borne in mind that the dose of allopurinol should be adjusted when azathioprine is co-administered due to the increase in 6-mercaptopurine levels and the possibility of toxic effects.

Cardiovascular effects – results from randomized clinical trials

It is logical to assume that if hyperuricemia has a pathogenetic role in cardiovascular pathology, its reduction will be associated with a lower cardiovascular risk. In recent years, drugs with hypouricemic effect have been shown to improve cardiovascular and renal function and slow the progression of pathomorphological changes. It has been suggested that uric acid may be a biomarker for metabolic disorders and a target in the prevention of metabolic syndrome and non-alcoholic hepatic steatosis.

Allopurinol improves endothelial function and NO production in heart failure and type 2 diabetes. Its direct hypouricemic effect is not strong, but reduces the level of free radicals. Reduces cardiovascular complications in patients with dilated cardiomyopathy. After coronary bypass, it reduces lipid

peroxidation. Its intake reduces left ventricular hypertrophy and clinical manifestations of heart failure. It improves vasodilatory capacity and blood volume, increases ATP levels and thus supplies the myocardium with energy. MCP-1 is a mediator of myocardial dysfunction and remodeling. It is involved in the pathogenesis and progression of heart failure. In rats with volume type heart failure, its myocardial expression is increased. There is evidence that allopurinol decreases the synthesis of MCP-1 in monocytes. Oxypurinol has a beneficial effect on the ejection fraction below 40%. In several studies, allopurinol or oxypurinol have been shown to reduce myocardial remodeling after myocardial infarction as well as left ventricular remodeling in animals with dilated cardiomyopathy. J. Hare et al. followed patients with moderate to severe heart failure treated with oxypurinol. They reported clinical improvement only in patients with a baseline serum uric acid level above 9.5 mg/dl. In patients with unstable angina pectoris treatment with allopurinol 600 mg/24 h has improved physical capacity. Contrary to these results, M. Givertz did not observe an improvement in functional capacity, quality of life and ejection fraction in the follow-up of 253 patients with chronic heart failure and hyperuricaemia receiving allopurinol. It is not clear what these differences are due to. In rats with induced hyperuricemia, allopurinol inhibits neointimal formation in the carotid arteries. Judging by the fact that the media and intima consist mainly of smooth muscle cells, it can be assumed that the drug inhibits smooth muscle cell proliferation.

Several short-follow-up studies have demonstrated the beneficial effect of allopurinol on the progression of chronic renal failure. The reduced dose in patients with grade 3-4 renal failure and gout may not lower serum uric acid levels below 6 mg/dl. Y. Siu et al. conducted a randomized study in 54 patients with hyperuricaemia and mild to moderate chronic renal failure. An improvement in renal function was observed in subjects treated with allopurinol for one year compared with controls. M. Goicoechea et al. studied 113 patients with hyperuricemia and chronic renal failure. At the end of the second year of follow-up, the glomerular filtration rate decreased by 3.3 ± 1.2 ml/min/1.73m² in the control group, while in the allopurinol-treated group it increased by 1.3 ± 1.3 ml/min/1.73m². In another randomized study, B. Shi et al. have tested the effect of the drug on 40 patients with IgA nephropathy. No improvement in renal function was reported after six months of treatment, but blood pressure improved.

A systematic review, including 9 studies and 476 participants, summarized the available evidence for the effect of urate-lowering treatment on the kidneys. In 5 of the studies, no significant change in eGFR was observed between patients taking allopurinol and control arms. In three studies, with a total of 130 participants, allopurinol intake decreased serum creatinine. There are insufficient data at this stage to recommend the use of allopurinol to delay chronic renal failure. Its use in diabetic mice reduces tubulointerstitial fibrosis. Allopurinol is thought to reduce mortality in patients with hypertensive nephropathy due to its protective effect on the vascular system. Randomized clinical trials are needed to confirm its positive effect in patients with hypertensive nephropathy in daily clinical practice.

Febuxostat

Febuxostat (Adenuric) is a non-purine xanthine oxidase inhibitor with higher selectivity for XO, which inhibits both oxidized and reduced forms of XO and lowers serum UA levels. At therapeutic concentrations it does not inhibit other enzymes involved in the metabolism of purines and pyrimidines – guanine deaminase, hypoxanthine-guanine phosphoribosyl transferase, orotate phosphoribosyl transferase, orotidine monophosphate decarboxylase or purinenucleoside phosphorilase.

Based on the third phase conducted studies – APEX, FACT, CONFIRMS and two additional open extended studies – EXCEL and FOCUS, in 2008 it was approved by the European Medicines Agency (EMA) for use in Europe, and in 2009 by the FDA – for the USA.

The results show a good effect in terms of tophi reduction. With a single daily dose of 80 mg in 83% of patients the size of the tophi decreases; at a dose of 120 mg daily the size of tophi reduces at 66%. The reason why the low dose of the drug gives better results is not clear. Its effect is better compared to the use of allopurinol.

Significantly higher numbers of febuxostat patients reached the desired serum UA level than those receiving allopurinol. The maximum dose of allopurinol was 300 mg/day, in some studies the dose was also lower depending on the degree of kidney damage (100 or 200 mg/ day).

Febuxostat is considered in case of failure to achieve target UA levels < 6 mg/dl (357 μ mol/l). It can be used in renal involvement (allopurinol administration is associated with a higher risk of toxicity). There is still insufficient clinical experience with the drug in patients with severe hepatic and renal insufficiency.

Its efficacy and safety in stage four chronic renal failure have been reported in one study, with no data available after renal transplantation. The clinical data of 73 patients with glomerular filtration ≤ 30 ml/1.73 m² (MDRD) at the start of febuxostat treatment were analyzed. Eighteen of them had a renal allograft. The mean duration of gout was 6 years. Renal function improved in 16 of the patients, did not change in 20 and worsened in 31. No cardiovascular events were reported during treatment. It can be concluded that the drug is effective in patients with grade 4-5 chronic renal failure, but its safety with respect to renal function of the allograft is unclear.

Comparative studies have shown that the toxicity of allopurinol and febuxostat is similar. On the other hand, the frequency of crises with the use of febuxostat is relatively higher, which is due to the faster and earlier reduction of serum UA levels.

The dose of febuxostat can be titrated from 40 to 120 mg daily until target serum UA levels are reached. In Europe it is allowed in the form of tablets of 80 mg and 120 mg.

Cardiovascular effects – results from randomized clinical trials

Febuxostat is a potent non-purine inhibitor of the oxidized and reduced form of the XO. In mouse models, it suppresses experimentally induced atherosclerosis. Blocks the formation of reactive oxygen radicals and inflammatory cytokines from cholesterol crystals. Unlike allopurinol, which is excreted by the kidneys, febuxostat is primarily metabolised in the liver. Its use in chronic renal failure rapidly lowers serum uric acid levels. In dogs with chronic heart failure, it improved left ventricular function, and in mouse models, it reduced systolic overload due to left ventricular hypertrophy. After cardiac surgery, it is more effective than allopurinol in lowering serum uric acid levels, reducing left ventricular hypertrophy and maintaining renal function. A. Nakagomi et al. conducted a prospective study in 66 patients with chronic heart failure and a mean left ventricular ejection fraction of $37 \pm 6.8\%$. Their aim was to compare the effect of febuxostat and allopurinol on inflammation and heart function. Thirty-one of the patients were treated with febuxostat and 30 with allopurinol. Both drugs have been shown to reduce left ventricular mass in patients with hypertension and ischemic heart disease. The distribution of NYHA patients was comparable between the groups. They have been on standard treatment including ACE inhibitors, angiotensin receptor blockers, beta-blockers, furosemide and

spironolactone, or a combination of these for a minimum of three years. The researchers found that treatment with febuxostat more strongly suppressed inflammation, improved endothelial function, preserved glomerular filtration and more strongly reduced serum uric acid, urinary microalbumin, CRP and MCP-1 without causing significant side effects.

Uricosurics

90% of gout cases are due to decreased urate excretion. In humans, physiologically 5-10% of filtered urate is excreted by the kidneys. Most is reabsorbed through the renal tubules.

Uricosurics are the first drugs used to treat gout. Any drug that in one way or another increases the excretion of UA in the urine is considered uricosuric. The main indication is when uric acid excretion does not meet the expected serum value and glomerular filtration rate. The cause can be primary or secondary.

Salicylates are the first drugs used to reduce UA. They have a paradoxical effect on the renal tubules – at low doses they reduce the excretion of UA, and at high doses they increase it.

Early clinical trials have shown that most uricosuric agents, including salicylates, probenecid, and sulfinpyrazone, are organic acids using a common transport system with UA at the level of the renal tubules. On a competitive basis, they inhibit UA reabsorption.

In recent years, the role of the so-called OAT (organic anion transporters) family located on the apical membrane of epithelial cells in the proximal renal tubules has been revealed. Several transporters have been found to be relevant to UA levels. Of these, most emphasis is on the uric acid transporter 1 – URAT1 and the glucose transporter – glucose transporter called GLUT 9. URAT1 is encoded by the SCL22A12 gene and is located on the apical membrane of epithelial cells in the proximal renal tubules. It is associated with the reabsorption of urate ions at the expense of organic anions. Most known uricosuric drugs suppress the function of this transporter, thereby reducing urate reabsorption. In contrast to uricosurics, diuretics increase the reabsorption of urate ions.

Benzbromarone is the drug with the best uricosuric effect known in clinical practice. It blocks URAT1 and inhibits the reabsorption of urate by epithelial cells.

Lesinurad is a novel selective inhibitor of uric acid reabsorption acting by inhibiting URAT1. It also inhibits OAT4, a transporter associated with diuretic-induced hyperuricaemia.

GLUT9 is a glucose-fructose protein transporter with a recently established role in urate metabolism. It is encoded by the SCL2A9 gene and exists in two isoforms located on the apical and basolateral membranes of the epithelial cells of the proximal renal tubules responsible for the reabsorption of urate ions. Its function is not related to organic anions and is weakly affected by benzbromarone, probenecid and losartan.

The examination of renal urate excretion should be considered to clarify the mechanism of hyperuricemia and to select patients suitable for treatment with uricosurics. It was introduced as a routine procedure in clinical practice by Prof. K. Kanev. The 24-hour urine test for urate, urate clearance, together with urinary creatinine and creatinine clearance, contribute to the assessment of renal function and the degree of urate excretion.

Medications approved for use in gout

Probenecid

- Mild to moderate inhibition of URAT1, GLUT9, OAT1 and OAT3 (transport UA across the basolateral membrane to the circulation)

- Good absorption after oral administration
- Peak plasma concentration on the fourth hour of its administration
- Dose-dependent effect within 6 to 12 hours, which determines the need for a double dose
- Metabolized in the liver
- Severe side effects are rare, skin rashes and gastrointestinal reactions have been observed in 20% of patients.

- Titrate the dose – start with 500 mg twice daily and gradually increase to 2 g daily when the tolerability is good. The maximum daily dose is 3 g daily.

Sulfinpyrazone

- Phenylbutazone analogue
- Inhibits URAT1
- Good absorption after oral administration
- Peak plasma concentration is achieved in the third hour.

- It is metabolized in the liver, more than 1/3 of the dose is excreted unchanged by the kidneys.

- It has been withdrawn from use in most countries due to its poor tolerance, antiplatelet properties and lack of effect at low levels of glomerular filtration rate.

Benzbromarone

- The strongest uricosuric drug in clinical practice
- Completely suppresses the activity of URAT1.
- Inhibits OAT1 and OAT3.

- Reaches a peak plasma concentration 2 to 4 hours after oral administration.

- Is metabolised in the liver to its active metabolite hydroxy-benzbromarone, with uricosuric effect and a half-life of 24 hours.

- No dose adjustment is required for renal impairment.

- Start with a dose of 50 mg/day in order to prevent mobilization gout crises, due to the rapid decrease in serum UA levels. The maximum daily dose is 200 mg/day.

- The effectiveness of 100 mg/day is better compared to allopurinol at a dose of 300 mg/day or probenecid – 1000 mg/day. The efficacy of the drug is close to that of allopurinol at a dose of 400 mg daily in patients with preserved renal function. Recent randomized controlled trials have shown that the efficacy of benzbromarone at a dose of 200 mg daily to achieve serum UA levels < 5 mg/dl is comparable to that of allopurinol at a dose of 600 mg/day.

- Unlike other uricosuric drugs, which have no effect on glomerular filtration below 50 ml/min, benzbromarone retains its uricosuric effect at glomerular filtration rate up to 20 ml/min, despite the concomitant use of diuretics and cyclosporine in transplant patients.

- Due to the frequent manifestations of hepatotoxicity, EMA limits the use of benzbromarone in many European countries.

Lesinurad (Zurampic)

- The first selective uric acid reabsorption inhibitor approved in the United States.

- Inhibits URAT1 and OAT4 transporter, the latter is associated with diuretic-induced hyperuricaemia.

- Approved by the EMA in February 2016 for use in combination with XO1 in patients who did not reach target serum UA levels with XO1 alone.

- The daily dose is 200 mg per os in combination with Allopurinol or Febuxostat.

- It is characterized by good plasma bioavailability and high level of plasma protein binding. The drug is metabolized by CYP2C9 – it must be applied with caution when co-administered with CYP2C9 inhibitors (eg fluconazole, amiodarone).

- Treatment of asymptomatic hyperuricaemia with this medicine is not recommended.

- It should not be used as monotherapy due to an increased risk of kidney damage.

- Starting treatment with Lesinurad may provoke gout crises. Their prevention is recommended.

- Its use is not discontinued in the event of a gout crisis.

Its approval in combination with xanthine oxidase inhibitors is based on three randomized, placebo-controlled studies involving 1,537 patients followed for 12 months. Patients treated with Lesinurad and Allopurinol or Febuxostat had significantly lower serum uric acid levels than placebo. In a randomized double-blind study in 227 patients with an inadequate response to Allopurinol, the addition of Lesinurad resulted in a significant decrease in serum uric acid levels. Its levels decreased by 16%, 22% and 30% with Lesinurad doses of 200, 400 and 600 mg, respectively. Similar results have been reported in patients with mild to moderate renal insufficiency.

- Need to change the dose for kidney damage as follows:

- CrCl ≥ 45 ml/min, no dose adjustment is required;

- CrCl <45 ml/min do not start Lesinurad;

- Discontinuation at CrCl < 45 ml/min;

- Renal function should be assessed prior to initiating treatment with Lesinurad and periodically during treatment;

- Lesinurad/Allopurinol (Duzallo) 200/200 mg and 200/300 mg

- Lesinurad/Allopurinol should not be combined with additional Lesinurad.

- Crisis prevention is needed in patients who have not taken Lesinurad before.

- Its use should be discontinued in the event of a gout crisis.

- Need to change the dose for kidney damage as follows:

- Mild to moderate (CrCl > 45 ml/min), no dose change required; Monitor CrCl more frequently if it is below 60 ml/min;

- Moderate to severe renal insufficiency (CrCl 30-45 ml/min): In these cases it should not be started. It should be discontinued if CrCl is consistently below 45 ml/min during treatment.

- Severe renal insufficiency (CrCl < 30 ml/min), end-stage renal disease, kidney transplant patients, dialysis patients: Contraindicated

- Dose adjustment in hepatic insufficiency

- ✓ Mild to moderate (Child-Pugh A and B): No dose adjustment required;

- ✓ Severe (Child-Pugh C): Safety and efficacy have not been established;

Many drugs – renofovir, emtricitabine, reverse transcriptase inhibitors are excreted by the kidneys via OAT1 and OAT3. Uricosurics such as benzbromarone and probenecid inhibit OAT1 and OAT3. In

such cases, treatment with lesinurad may help to avoid adverse drug interactions.

Uricosuric drugs that are not standard in clinical practice and are used „off label“: fenofibrate, losartan, atorvastatin, leflunomide, ketazone

Their use may improve the ability to reach the target values of serum UA in patients with concomitant pathology for which they are prescribed and may have a role as an adjuvant ULT.

The use of „adjuvant ULT“ is suitable in the presence of concomitant diseases, and in cases where serum UA values are at the upper-limit, close to the target ULT levels. The possibility of drug interactions should also be considered. An example of this is fenofibrate with colchicine. The simultaneous application increases the risk of drug-induced myopathy with/without rhabdomyolysis.

Adequate treatment of hyperuricemia with uricosuric agents requires not only proper selection of patients for this type of therapy, but also systematic monitoring of the effect and the occurrence of side effects (especially urolithiasis). In this direction the examination of renal function is of major importance. Uric acid clearance above 6 ml/min/1.73 m² body surface area is considered an independent risk factor for urolithiasis in uricosuric therapy.

In this regard, patients with a history of calcium oxalate lithiasis are also at risk due to increased urate excretion, especially at low urinary pH. Accumulated kidney stones are mostly composed of uric acid, not from urate.

Uric acid salts are more soluble than uric acid itself. Alkalization of the body and urine increases the solubility of UA, dissolves crystals and increases excretion. This helps to treat and prevent urate lithiasis. Preparations that can be used in this direction are Alkalurin, Neoralit SR, Basica.

Hydration of the body is also important – fluid intake of at least 2-2.5 liters per day. Preferred are alkaline mineral waters with a pH > 8, which can be alternated with neutral waters.

In gout with tophi, the risk of manifest urolithiasis is not high. With the intake of uricosurics, the dissolution of the tophi does not occur suddenly, but gradually. This ensures a smoother excretion of uric acid through the renal tubules.

When the value of glomerular filtration rate is less than 50 ml/min, the effect of probenecid, sulfinpyrazone and lesinurad is lost, while benzbromarone can be effective at glomerular filtration rate up to 20 ml/min.

In patients with increased uric acid production undergoing XO1 therapy, the total amount of UA fil-

tered through the glomeruli is reduced. Due to this, from a practical point of view, the initial therapy in patients with insufficient urate excretion is XO1. If the target UA values are not reached, uricosuric medication and/or a combination of XO1 with uricosuric (according to EULAR 2016) is administered at a low dose with a tendency to gradually increase the dose until the required serum levels are reached. The recommendation to combine XO1 with uricosuric is based on uncontrolled studies showing that probenecid-allopurinol or benzbromarone-allopurinol are more effective than allopurinol monotherapy. The combination of lesinurad-allopurinol is also promising, according to the results of a phase II clinical trial.

Key ACR recommendations

In 2012, the ACR developed the following key recommendations to make it easier for GPs and rheumatologists to choose uricosuric therapy and to monitor patients:

- As monotherapy Probenecid is the uricosuric drug of first choice. In patients with creatinine clearance < 50 ml/min is not suitable as first-line uricosuric therapy (level of evidence B).
- The use of drugs other than probenecid with a clinically significant uricosuric effect, such as fenofibrate and losartan as a component of uricosuric therapy, may be of therapeutic benefit.
- History of urolithiasis is a contraindication to uricosuric therapy.
- Serum UA levels should be determined before initiating uricosuric therapy.
- Elevated levels of UA in the urine are an indicator of its overproduction and are a contraindication for uricosuric therapy.
- Monitoring of UA levels is mandatory during uricosuric therapy.
- In order to reduce the risk of urolithiasis, urinary alkalization (eg with potassium citrate) with monitoring of urine pH should be considered, in addition to increased fluid intake.

Uricolytic therapy

Uricase is responsible for the transformation of UA into 5 to 10 times more soluble allantoin. In humans and some primates, due to two independent mutations in the gene encoding urate oxidase, such a transformation does not occur, and the end product of purine metabolism is UA. Due to this the plasma and tissue content of UA is 5 to 10 times higher in humans than in mammals which express uricase.

Pegloticase is a recombinantly modified uricase used to treat severe, refractory cases of gout, with insufficient effect from conventional ULT administered at

optimal doses. Approved by the FDA in 2010, pegloticase therapy is not recommended as a first-line ULT.

It is given at two to four weeks as an intravenous infusion, at a dose of 8 mg dissolved in 250 ml of saline.

Clinical trials lasting 6 months found that in 38-48% of patients treated with pegloticase at two-week intervals and in 20-49% of patients applying the drug at four-week intervals the desired serum level of UA was reached. Of these, 42% and 35% respectively retained the achieved effect. In 40% and 21% of the patients, respectively, complete disappearance of the tophi was observed. However, the formation of antibodies to the drug is possible. It is the reason for the loss of the plasma effect of the treatment by the third month of its application. There is no consensus on the duration of treatment, but according to EULAR rec-

ommendations from 2016, switching to oral ULT can be considered after the complete disappearance of tophi. Due to the high risk of infusion reactions, pre-medication with antihistamines and corticosteroids is required before administration of Pegloticase. Compared to the other urate-lowering drugs the frequency of gout crises is significantly higher. The drug is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency because a risk of hemolysis and methaemoglobinaemia exists. In some ethnic groups, this defect is more common, which requires screening before initiation of therapy.

Serum UA levels should be monitored before each infusion. If they are maintained above 6 mg/dl ($> 360 \mu\text{mol/l}$), the infusion is stopped due to an increased risk of infusion reactions and anaphylaxis.

2016 EULAR RECOMMENDATION FOR THE MANAGEMENT OF HYPERURICEMIA IN PATIENTS WITH GOUT

Fig. 1 Treatment of hyperuricaemia in patients with gout according to EULAR 2016 guidelines

Guidelines for anti-inflammatory pharmacological prevention of acute crises at the onset of ULT

The early increase in acute attacks at the onset of ULT is thought to be the result of remodeling of intra-articular urate crystal deposits as a consequence of the rapid and significant decrease in the urate concentration.

Experts believe that the need for prevention of acute gout crises should be discussed with each patient. In individuals who refused prophylaxis of crises with slow titration of ULT, no statistically significant increase in acute attacks was observed. Most of the experts believe that low starting doses of ULT, with a slow increase in dosage are the basis for the prevention of attacks (start low, go slow). However, because of the high frequency of attacks, initiation of prophylaxis is recommended. Due to the risk of serious side effects the need for a targeted examination of renal involvement prior to prescribing Colchicine as well as concomitant administration with statins and inhibitors of P-glycoprotein and/or CYP3A4 inhibitors is emphasized. The recommended duration of prophylaxis is 6 months. It is carried out with Colchicine at a dose of 0.5-1 mg/24 h, and the dose should be reduced in cases of renal involvement.

There is no consensus on when exactly to start ULT after an acute gout attack. According to ACR recommendations from 2012, ULT can be initiated during the acute phase if anti-inflammatory treatment has already been started. This is not recommended by the 2016 EULAR expert group, which does not provide specific guidance on when to start ULT. Two small clinical trials showed that initiation of allopurinol during a gout crisis did not prolong the crisis or make it more severe than delayed treatment.

In case of intolerance or contraindications to the use of colchicine, a low dose of NSAIDs should be considered (in the absence of contraindications). These are the drugs of first-line. They do not always manage to prevent all gout attacks after starting ULT.

Colchicine has rapid intestinal absorption, t_{max} 2 h, $t_{1/2}$ 4 h and enterohepatic cycle, contributing to its gastrointestinal toxicity. Colchicine binds irreversibly to dimers of the intracellular protein tubulin. Inhibits its polymerization and the formation of leukocyte microtubules. Inhibits granulocyte migration, phagocytosis of urate crystals and weakens the inflammatory response. It also stops the synthesis of leukotrienes.

As an alternative prophylaxis in patients with intolerance to or contraindications for colchicine and NSAIDs, the ACR recommends a low dose of pred-

nisone or prednisolone (specified as ≤ 10 mg/day). The use of higher doses to prevent attacks is considered inappropriate.

There is no consensus on the benefit/risk balance for the off-label administration of IL-1 inhibitors as an anti-inflammatory disease prevention in subjects with no therapeutic effect, intolerance or contraindications to low-dose colchicine, NSAIDs or corticosteroids.

Several studies have described the efficacy of canakinumab and rilonacept in preventing attacks when initiating allopurinol treatment. However, none of these drugs has been approved for prevention.

TREATMENT OF ACUTE GOUT CRISIS

General principles

According to the expert opinion, due to the high frequency of concomitant diseases and accompanying therapy in gout patients, the choice of treatment for crisis is based on the presence or absence of contraindications. One study found that more than 90% of patients had at least one contraindication for NSAIDs, and about a third of individuals prescribed colchicine had at least one major contraindication.

Colchicine is effective when given within 12 hours of the onset of symptoms, and there is general agreement that early initiation of any treatment for an articular crisis results in better efficacy. That is why in fully informed patients the working group recommends the "pill in the pocket" approach for the treatment of joint crisis.

According to the recommendations of EULAR 2016:

- first-line treatment of the acute crisis is colchicine (within 12 hours of the onset of complaints) at a loading dose of 1 mg, followed 1 hour later by 0.5 mg on day 1 and/or NSAIDs (plus an inhibitor of proton pump if necessary), oral corticosteroids (30-35 mg/day prednisolone – equivalent for 3-5 days) or arthrocentesis and local injection of corticosteroids (in monoarthritis and in easily accessible joints).

- Colchicine and NSAIDs should be avoided in patients with severe renal impairment.

- Colchicine should not be administered in patients receiving strong P-glycoprotein and/or CYP3A4 inhibitors such as cyclosporine or clarithromycin.

A double-blind randomized study showed that prednisolone (35 mg/day for 5 days) was as effective as naproxen (500 mg/twice daily for 5 days).

A recent study showed that prednisolone – 30 mg/day for 5 days had the same effect as indomethacin.

IL-1 inhibitors should be considered in patients with frequent crises and contraindications for Colchicine, NSAIDs and corticosteroids (oral or injectable),

In patients with contraindications, intolerance or not responding to treatment with NSAIDs and/or Colchicine, Canakinumab which is a 150 mg subcutaneous monoclonal antibody has demonstrated a better effect than subcutaneous daily application of 40 mg triamcinolone acetonide in reducing pain. In 2010, an eight-week double-blind study showed that Canakinumab provided rapid and lasting pain relief in patients with acute gout crises who did not respond to NSAIDs and Colchicine.

Anakinra- IL-1 receptor antagonist administered subcutaneously at a dose of 100 mg for 3 consecutive days is also effective in reducing joint pain during crisis.

Rilonacept, a soluble receptor antagonist that binds IL- β and IL-1 α at a dose of 320 mg, showed no significant difference compared to indomethacin at a dose of 50 mg – 3 times daily for 3 days.

Due to the risk of developing sepsis, experts do not recommend therapy with IL-1 blockers in the presence of infection, and emphasize the need for screening for occult ones. As soon as the acute crisis is cured with the IL-1 blocker in connection with the EMA's approval of canakinumab, the expert group emphasized the need to effectively reduce UA levels in patients with severe gout.

Assessment of the severity of the attack

Monotherapy with NSAIDs, systemic corticosteroids or colchicine is indicated in mild to moderate pain and in engagement of one or more small joints and one or two large joints. The use of a combination of medications is necessary in severe pain, in polyarticular involvement or in the engagement of very large joints.

There is a consensus that NSAIDs, colchicine and corticosteroids (intra-articular, oral or intramuscular) are equally effective in the treatment of acute gout attacks and the choice of therapy should be tailored to the individual needs of patients and the safety profile of the drug. Although paracetamol is not recommended as a first-line, it may be useful as an additional analgesic.

Numerous studies have been conducted to evaluate the effect of treatment for acute gout attacks. The results showed that low doses of colchicine (total dose 1.8 mg for 24 h) were more effective than placebo and were just as effective as high doses (total dose 4.8 mg), but had a significantly better safety profile.

Colchicine is an appropriate first-line treatment for an acute attack, but within the first 12 hours af-

ter the onset of complaints according to EULAR, 36 hours according to ACR, provided that the patient has not received prophylactic treatment with this drug in the last 14 days.

A loading dose of 1.2 mg was used, followed by 0.6 mg after one hour. After the 12th hour, a dose of 0.6 mg is given once or twice a day until the crisis is completely resolved.

In countries where the available dosage form of colchicine is in doses of 0.5 and 1 mg, as in Bulgaria, a loading dose of 1 mg and 0.5 mg after one hour can be used. If necessary, colchicine therapy continues after 12 hours (0.5 mg up to three times a day), until the attack resolves.

The therapeutic range of colchicine is up to 6 mg/day, and toxic – over 6 mg/day, but diarrhea can occur at doses below 6 mg/day.

For patients who have undergone prophylactic treatment with colchicine in the last 14 days, it is necessary to conduct therapy with other drugs – NSAIDs or corticosteroids.

There is no conclusive evidence from comparative studies between NSAIDs and placebo. NSAIDs (conventional or selective COX-2 inhibitors) have comparable effects.

For the treatment of acute pain and/or gout crisis, the use of the full, FDA or EMA approved anti-inflammatory/analgesic dose is recommended.

Naproxen, indomethacin and sulindac are approved by the FDA for the treatment of acute gout. However, other NSAIDs in analgesic and anti-inflammatory doses may be equally effective. For COX-2 inhibitors, as a therapeutic option in patients with GI contraindications or intolerance to NSAIDs, published randomized controlled trials support the efficacy of etoricoxib and lumiracoxib, but these agents are not approved for use in the United States, furthermore lumiracoxib has been withdrawn from use in some countries due to hepatotoxicity.

In recent years, a number of NSAID families have evolved. NSAIDs with fewer side effects and good clinical results have emerged.

There is currently no consensus on the use of intramuscular ketorolac or topical NSAIDs to treat an acute gout crisis.

The patient's education should aim to teach him what to do during the first hours of the crisis: 1. To start therapy with colchicine and NSAIDs (colchicine alone is not enough in a crisis). 2 Stop uricolytic therapy. 3 Apply cold compresses; 4. Do not heat or lubricate in order to heat the joint; 5. Do not start aspirin or antibiotics alone; 6. In case of swelling of a large joint, seek help immediately.

Systemic and intra-articular administration of corticosteroids and adrenocorticotrophic hormone (ACTH).

When choosing corticosteroids as initial therapy, the number of joints with active arthritis must first be assessed. If one or two joints are affected, oral administration is appropriate; when the pathological process engages one or two large joints, corticosteroids can be applied intraarticularly.

In the case of intra-articular injection of corticosteroids, their dose is determined by the size of the affected joint or joints, and this approach is combined with oral administration of corticosteroids, NSAIDs or colchicine.

When intra-articular administration is not appropriate – polyarticular involvement, patient preference or when this manipulation is not routine for the specialist, then oral administration of corticosteroids is recommended.

An alternative intake of corticosteroids is also possible – full dose for 2-5 days, with gradual dose reduction for 7-10 days and discontinuation of treatment.

In patients who are unable to take oral medications due to surgery or other conditions in consideration is the use of intra-articular, intramuscular/intravenous methylprednisolone equivalent to 30-35 mg prednisolone.

In such cases, subcutaneous injection of ACTH is also possible, which is an old practice. If necessary, these drugs can be re-administered, the subsequent doses are determined based on the initially achieved therapeutic effect.

These drugs stimulate the synthesis and release of corticosteroid hormones. They are used in diagnostic tests to distinguish primary adrenal insufficiency from secondary adrenal insufficiency. They have limited therapeutic value.

Cosyntropin (Cortrosyn) is an adrenocorticotrophic hormone (corticotropin) that stimulates the production and release of endogenous steroids. It is given in acute gouty arthritis, in postoperative patients and in patients who cannot take medication orally.

Dose

- Powder for injection 0.25 mg/vial;
- Screening for adrenocortical insufficiency 0.25-0.75 mg directly intravenously/intramuscularly.

There is still no consensus on intramuscular injection of ketorolac or triamcinolone in people with an acute gout attack and inability to take oral medication.

Initial combination therapy

For patients with severe gout crisis ($VAS \geq 7$) and patients with acute polyarthritis or involvement of more than one large joint, initial concomitant use in full doses (or, where appropriate, a full dose of one and a prophylactic dose of the other agent) of two of the pharmacological options recommended above can be administered. Especially given the combined use of colchicine and NSAIDs, oral corticosteroids and colchicine or intra-articular corticosteroids with each of the other options. The combined use of NSAIDs and systemic corticosteroids has not been discussed because of existing concerns in their synergistic toxic effects on the gastrointestinal tract.

Hydration and alkalization of the body are very important.

Evaluation of response to treatment

With a favorable response to therapy, the next step is to educate the patient and assess the need for ULT.

In case of unsatisfactory response to treatment, it is necessary to change the drug, use a combination of drugs, and in the absence of a favorable therapeutic effect – application of drugs that have not yet been approved for use.

The inadequate response of an acute gout attack to pharmacological therapy is defined on the basis of the following criteria: improvement with less than 20% in the pain score within 24 hours after initiation of therapy or improvement of this indicator by less than 50% after 24 hours from the start of treatment.

In such cases, the possibility of a misdiagnosis should be considered. In cases of an acute gout attack refractory to other medications, an IL-1 inhibitor such as anakinra (100 mg subcutaneously once daily for three consecutive days) or canakinunab (150 mg subcutaneously) may be used.

However, due to the lack of randomized trials with anakinra and the unclear benefit/risk balance, the lack of US FDA approval of canakinunab, the role of IL-1 inhibitors is considered uncertain.

2016 EULAR RECOMMENDATION FOR THE MANAGEMENT OF FLARES IN PATIENTS WITH GOUT

Fig. 2. Treatment of acute gout crisis according to EULAR 2016 guidelines

TREATMENT OF HYPERURICEMIA AND GOUT IN KIDNEY TRANSPLANT RECIPIENTS

Data from clinical trials do not support the widespread use of urate-lowering drugs in recipients of renal allograft with hyperuricemia. Urate-lowering therapy should be used in patients with gout. Beneficial effects have been reported in patients with severe hyperuricaemia above 8 mg/dl. Nephroprotection is achieved at a serum uric acid level below 6.8 mg/dl.

Anti-inflammatory therapy should begin with the diagnosis of gouty arthritis. Colchicine is effective in most patients. They have a high risk of drug-induced myoneuropathy. Impaired renal function favors its development, therefore a sparing regimen is needed (Table 6).

NSAIDs are an alternative to colchicine in the treatment of gouty arthritis, but they have an adverse effect on renal hemodynamics and can cause hyperkalaemia. Similar changes in hemodynamics occur with cyclosporine. Therefore, NSAIDs should be used

Table 6. Doses of colchicine to control gout crisis in kidney transplant patients

Day	Dosage regime
1	Colchicine 2 times 0.6 mg/24 h. stops when diarrhea occurs
2	Colchicine 2 times 0.6 mg/24 h. stops when diarrhea occurs
3 to 10	Colchicine 2 times 0.6 mg/24 h. stops when diarrhea occurs

with extreme caution in transplant patients. Some kidney-sparing drugs, such as sulindac or COX-2 inhibitors, may be prescribed. It should be borne in mind that at low doses NSAIDs suppress the excretion of uric acid and its plasma concentration increases. Medium doses are neutral and high doses are uricosuric. Weekly monitoring of renal function is required for treatment with more potent NSAIDs. Most transplant patients are on low-dose corticosteroids. In the onset of a gout crisis, their dose may be increased to 0.5-1 mg/kg/24 h. for 3 to 7 days, then reduced to a maintenance dose within 14 days. Adrenocorticotrophic hormone at a dose of 40-80 IU intramuscularly is an alternative to prednisolone.

Urate-lowering therapy includes allopurinol at a dose of 100-200 mg/24 h. Allopurinol slows down the metabolism of azathioprine. When it is administered, the dose of azathioprine should be reduced by 25-50% and the blood count should be monitored regularly. Combining allopurinol with mycophenolate mofetil is safer. Mycophenolate mofetil inhibits only the de novo pathway of purine synthesis, with allopurinol having no effect on its metabolism.

F. Perez-Ruiz and his team followed 1,328 transplant patients for one year and found that both drugs allopurinol and benzbromarone were effective in controlling hyperuricemia, but benzbromarone led to a more significant decrease in serum uric acid. They summarized that benzbromarone at a dose above 75 mg/24 h. is more effective than allopurinol by reducing the risk of azathioprine interaction with allopurinol.

When prescribing these drugs, it should be borne in mind that the urate-lowering effect of allopurinol does not depend on renal function. Uricosuric drugs are not effective in significant renal graft dysfunction and creatinine clearance < 30 ml/min. During treatment with cyclosporine and while taking probenecid, patients should be monitored regularly for the risk of developing nephrocalcinosis. Patients with uric acid excretion in 24-hour urine > 750 mg should drink more fluids and alkalize the urine. Cyclosporine-induced hyperuricaemia is reversible. Replacement of cyclosporine with tacrolimus is associated with a lower risk of developing hyperuricaemia.

The studies conducted by Sofue et al. and Tojimbara et al. have shown that a large proportion of renal transplant patients with hyperuricaemia treated with low dose Febuxostat 10-20 mg/24 h. reach target serum uric acid levels and stable eGFR values. No serious adverse events and no change in liver function were reported. There was also no alteration in the serum levels of immunosuppressive drugs. The latest study in transplanted patients with emerging hyperuricemia was conducted by Shen et al. They found that Febuxostat caused a significantly faster drop in uric acid than Allopurinol, but in the long run the two drugs had a similar effect.

ASSESSMENT OF QUALITY OF LIFE

There are a small number of studies evaluating the quality of life in gout. They are cross-sectional, hospitalized patients are included and generic questionnaires are used. The most commonly applied questionnaires are the Health Assessment Questionnaire Disability Index (HAQ-DI) and Short Form 36 (SF-36), (Table 7 and Table 8). The results are that patients with gout have a poorer quality of life compared with controls, even after assessing the concomitant pathology. Some authors have found that serum uric acid levels and tophi affect quality of life, while others have not confirmed it. Specific characteristics such as the incidence of gout crises, intensity, pain in the intercritical period, greater number of affected joints and concomitant morbidity are associated with deteriorated quality of life. A cohort study is needed in pre-hospital care, where most gout patients are treated, in order to determine the factors that lead to deterioration in the quality of life over time. This will make it possible to early identify people at increased risk.

The HAQ-DI and SF-36 questionnaires are generic, not disease-specific. They are developed for the complex assessment of patients with rheumatic diseases: rheumatoid arthritis, osteoarthritis, systemic lupus erythematosus, systemic sclerosis, ankylosing spondylitis, fibromyalgia, psoriatic arthritis. They are also used in patients with HIV. The HAQ-DI

questionnaire has 8 sections: dressing, getting up, eating, walking, personal hygiene, reaching for objects, grabbing and other activities.

There are 2 or 3 questions in each section, the score varies from 0 (no difficulty) to 3 (inability to perform the action). The final score of each of the eight areas is the highest score, for exam-

ple if one of the questions is rated 1 and another 2, then the score in this section is 2. If an aid or companion assistance is required, the minimum score in that section is 2. The eight scores of the eight sections are summed and divided by 8. If one of the sections is not filled, the sum of the scores is divided by 7.

Health Assessment Questionnaire (HAQ-DI)

Table. 7 Generic health assessment questionnaire – Health Assessment Questionnaire –Disability Index (HAQ-DI).

Please note the answer that best describes your ability to perform your usual activities during the past week:

	Without any difficulty	With some difficulty	With great difficulty	I can not do it
Getting dressed Would you be able to:				
Getting dressed, including tying your shoelaces and buttoning up your buttons?				
Washing your hair?				
Getting up Would you be able to:				
Getting up from an ordinary chair?				
Getting up and laying down in bed?				
Eating Would you be able to:				
Cutting meat in a plate?				
Lift a full bowl or glass to your mouth?				
Open a carton of fresh milk?				
Walking Would you be able to:				
Walking outside on flat terrain?				
Climb five steps?				

Please note those aids or accessories that you normally use in each of the above activities:

- walking stick
- accessories used for dressing (hook for fastening, extension of buttons or zipper, shoe with long handle, etc.)
- walker (for people with
- specially adapted utensils/for cooking and/or eating / motor difficulties)
- crutches
- specially adapted chair
- wheel chair
- others (specify: _____)

Please mark those categories for which you usually need the help of another person:

- getting dresses
- eating
- getting up
- walking

	Without any difficulty	With some difficulty	With great difficulty	I can not do it
Personal hygiene Would you be able to:				
Wash and dry your body?				
Take a bath?				
Sit down and get up from the toilet?				
Reaching objects Would you be able to:				
Reach for and lower an object weighing 2.5 kg (eg a bag of potatoes) above your head?				
Bend down to lift clothes off the floor?				
Catching Would you be able to:				
Open a car door?				
Open jars that have already been opened?				
Unscrew and turn on the taps?				
Activities Would you be able to:				
Do things (go to the post office, the bank, etc.) and go shopping?				
Getting in and out of a car?				
Do housework like vacuuming or gardening?				

Please note those **aids or gadgets** that you usually use in each of the above activities:

- raised toilet bowl
- handle next to the bath tub
- seat in the bath tub
- devices with a long handle for reaching objects
- jar opener
- fixtures with a long handle for the bathroom (like a brush for washing the back) (for jars previously opened)
- others, specify (_____)

Please mark those categories for which you usually need the help of another person:

- personal hygiene
- grabbing and opening different things
- reaching objects
- shopping and house work

Questions added to HAQ

What degree of stiffness have you had due to your illness in the past week? Place a mark on the line to show the severity of your stiffness.

0 _____ 100
There is no stiffness Very severe stiffness

The Short Form – 36 questionnaire reported eight areas (physical activity, pain, activity limitations due to physical health problems, activity limitations due to emotional problems, emotional well – being, ability to work/fatigue, general health perceptions). There is also a section in which the subject himself determines the change in his health.

Each question is evaluated on a scale from 0 to 100. The questions have the same weight – the lower the score, the more pronounced the damage and vice versa – the higher the score, the milder the impairment. A score of 0 is equivalent to a maximum impairment, while a score of 100 reflects the absence of an impairment.

Table 8 Generic health assessment questionnaire – Short Form – 36 (SF-36) Questionnaire V1.**Short Form – 36 Questionnaire V1**

This questionnaire contains questions related to your assessment of your health. The answers to the questions give us the opportunity to understand how you feel and how well you cope with your usual load.

When answering the questions, enclose the statement that most accurately reflects your opinion or condition.

How would you assess the state of your health in general? **(enclose only one digit)**

- Excellent..... **1**
 Very good **2**
 Good..... **3**
 Satisfactory..... **4**
 Bad **5**

How would you assess the state of your health in general now, compared to your health a year ago? **(enclose only one digit)**

- Much better than 1 year ago **1**
 A little bit better than 1 year ago..... **2**
 The same as 1 year ago..... **3**
 A little bit worse than 1 year ago **4**
 A lot worse than 1 year ago..... **5**

The following questions are about activities that you would do on a typical day. Does your health limit you now in performing the activities listed below? If so, to what extent? **(enclose only one digit from each line).**

Type of physical activity (load)	Yes, it limits me a lot	Yes, it limits me a little	No, it doesn't limit me at all
A. <u>Heavy physical exertion</u> such as: running, lifting heavy objects, doing strength sports.	1	2	3
B. <u>Moderate physical activity</u> such as: moving a table, vacuuming, working in the garden.	1	2	3
C. Lifting or carrying a bag of groceries.	1	2	3
D. Climbing <u>several</u> floors by stairs.	1	2	3
E. Climbing one floor by stairs.	1	2	3
F. Bending, kneeling or squatting.	1	2	3
G. Walking more than <u>1.6</u> kilometers.	1	2	3
H. Walking a <u>few hundred</u> meters.	1	2	3
I. Walking up to <u>a hundred</u> meters.	1	2	3
J. Self-bathing or dressing.	1	2	3

Has your physical health, in the last 4 weeks, caused difficulties in your work or in performing other usual daily activities? **(enclose only one digit from each line).**

	All the time	Most of the time	Sometimes	Rarely	Never
A. Have you had to reduce the time you spend at work or spend on other activities.	1	2	3	4	5
B. Have you done less work than you would like?	1	2	3	4	5
C. Have you been restricted in the type of work or other activities.	1	2	3	4	5
D. Did you have difficulties in performing your work or other activities (for example, additional efforts were required)	1	2	3	4	5

Has your emotional state (depression, anxiety), in the last 4 weeks, caused difficulties in your work or in performing other usual daily activities? (enclose only one digit from each line).

	All the time	Most of the time	Some-times	Rarely	Never
A. Have you had to reduce the time you spend at work or spend on other activities.	1	2	3	4	5
B. You have managed to do less work than you would like.	1	2	3	4	5
C. You have not performed your work or other activities as carefully as usual.	1	2	3	4	5

To what extent have your physical health or emotional state, in the last 4 weeks, interfered with your normal social contacts with family, friends, neighbors or the team?

- Does not interfere at all1
 A little.....2
 Moderate3 (enclose only one digit)
 Strong.....4
 Very strong5

How much physical pain have you had in the last 4 weeks?

- None.....1
 Very weak.....2
 Weak3
 Moderate4 (enclose only one digit)
 Strong.....5
 Very strong6

To what extent has the sensation of pain, during the last 4 weeks, interfered with your normal work (at home and away from home)?

- Does not interfere at all1
 A little.....2
 Moderate3 (enclose only one digit)
 Strong.....4
 Very strong5

These questions are about how you felt and what your mood was in the last 4 weeks. Please, for each of the questions, indicate this answer, which most accurately shows how you felt, what part of the time in the last 4 weeks (enclose only one digit from each line)

	All the time	Most of the time	Sometimes	Rarely	Not once
A. Did you feel refreshed?	1	2	3	4	5
B. Were you very nervous?	1	2	3	4	5
C. Did you feel so depressed that nothing could cheer you up?	1	2	3	4	5
D. Did you feel calm and balanced?	1	2	3	4	5
E. Did you feel full of energy?	1	2	3	4	5
F. Did you feel unhappy and sad?	1	2	3	4	5
G. Did you feel exhausted?	1	2	3	4	5
H. Were you a happy person?	1	2	3	4	5
I. Did you feel tired?	1	2	3	4	5

During what part of the last 4 weeks, did your physical health or emotional state interfere with your active communication with people (visiting friends, relatives, etc.)?

- All the time.....1
 Most of the time2
 Sometimes3 (enclose only one digit)
 Rarely4
 Not once5

How TRUE or FALSE is each of the following statements to you?
(enclose only one digit from each line)

	Definitely true	Rather true	I do not know	Rather false	Definitely false
A. It seems to me that I tend to get sick more than others.	1	2	3	4	5
B. My health is not worse than that of most of my acquaintances.	1	2	3	4	5
C. I expect my health to deteriorate.	1	2	3	4	5
D. My health is excellent.	1	2	3	4	5

Thank you for the answers!

Each question is evaluated from 0 to 100. The answers from one area are averaged together and 8 scales are formed. On the table. 9 are given grouped questions that are averaged to create each scale. Unanswered questions are not taken into account when calculating the score. Thus, the scores are the average of all responses in the relevant area to which the subject responded.

Table 9. Grouping of questions that are averaged together

Number of questions	Number of answers to the relevant questions	A value that is reported for each answer
1,2,20,22,34,36	1→	100
	2→	75
	3→	50
	4→	25
	5→	0
3,4,5,6,7,8,9,10,11,12	1→	0
	2→	50
	3→	100
13,14,15,16,17,18,19	1→	0
	2→	100
21,23,26,27,30	1→	100
	2→	80
	3→	60
	4→	40
	5→	20
	6→	0
24,25,28,29,31	1→	0
	2→	20
	3→	40
	4→	60
	5→	80
	6→	100
32,33,35	1→	0
	2→	25
	3→	50
	4→	75
	5→	100

Table 10. Averaging the responses from each scale formation area

Scale	Number of questions	After calculation according to table, average the following questions
Physical functioning	10	3,4,5,6,7,8,9,10,11,12
Restrictions due to physical health problems	4	13,14,15,16
Limitations due to emotional problems	3	17,18,19
Working capacity/Fatigue	4	23,27,29,31
Emotional well-being	5	24,25,26,28,30
Social activities	2	20,32
Pain	2	21,22
General health	5	1,33,34,35,36

Example: Questions 20 and 32 are used to evaluate social activities. There are 5 possible answers to each of them. A high score (answer № 5) of the 20 question reflects restrictions on social activities, while a high score (answer № 5) of 32 question reflects a lack of restriction on social functioning. From table 9 it can be seen that from the first to the fifth answer of the question 20 the values 100, 75, 50, 25 and 0 correspond. While the answers from the first to the fifth in question 32 correspond to the values 0, 25, 50, 75 and 100. On table 10 it is presented that the answers to these two questions are averaged in order to form the scale of social activities. If the subject has failed to answer some of them, then the score is equal to the question to which there is an answer.

In conclusion:

1. Timely diagnosis of gout is the basis of proper treatment and prevention of complications.
2. Educating patients to change their lifestyle is an essential part of the overall healing process.
3. The gout crisis should be treated and asymptomatic hyperuricemia should be monitored systematically.

4. In the presence of indications for ULT, treatment with the first group of drugs in a low dose is started, titrating the dose until the desired effect is achieved. Treatment begins outside the crisis.

5. In case of intolerance, insufficient effect or contraindications, uricosuric therapy or combination therapy – uricoinhibitor plus uricolimator is started.

6. Alkalization of urine and intake of sufficient fluids – alkaline mineral water helps dissolve the formed crystals and improves urate excretion.

7. It is desirable to remove large or multiple tophi surgically due to the fact that they are deposits of MSU crystals and damage the movements and structure of the joints.

References

- Abraham A, Drory VE. Influence of serum uric acid levels on prognosis and survival in amyotrophic lateral sclerosis: a meta-analysis. *J Neurol* 2014; 261:1133-8.
- Alloway JA, Moriarty MJ, Hoogland YT, Nashel DJ. Comparison of triamcinolone acetonide with indomethacin in the treatment of acute gouty arthritis. *J Rheumatol* 1993; 20(1):111-3.
- Altman RD, Honig S, Levin JM, Lightfoot RW. Ketoprofen versus indomethacin in patients with acute gouty arthritis: a multicenter, double blind comparative study. *J Rheumatol* 1988; 15(9):1422-6.
- Amado LC, Saliaris AP, Raju SV, et al. Xanthine oxidase inhibition ameliorates cardiovascular dysfunction in dogs with pacing-induced heart failure. *J Mol Cell Cardiol*. 2005; 3 531-6.
- Anzai N, Ichida K, Jutabha P, et al. Plasma urate level is directly regulated by a voltage-driven urate efflux transporter URATv1 (SLC2A9) in humans. *J Biol Chem* 2008; C800:156-200.
- Baldwin W, McRae S, Marek G, et al. Hyperuricemia as a mediator of the proinflammatory endocrine imbalance in the adipose tissue in a murine model of the metabolic syndrome. *Diabetes*. 2011; 60:1258-69.
- Baraf HS, Becker MA, Edwards NL, et al. Tophus response to pegloticase (PGL) therapy: pooled results from the GOUT 1 and GOUT2, PGL phase 3 randomized, double blind, placebo-controlled trials [abstract]. *Arthritis Rheum* 2008; 58(Suppl. 9):S22.
- Bastow MD, Durrington PN, Ishola M. Hypertriglyceridemia and hyperuricemia: effects of two fibric acid derivatives (bezafibrate and fenofibrate) in a double-blind, placebo-controlled trial. *Metabolism*. 1988; 37(3): 217-20.
- Becker MA et al. Determinants of the clinical outcomes of gout during the first year of urate-lowering therapy. *Nucleosides Nucleotides Nucleic Acids* 2008; 27:585-9.
- Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res Ther* 2010; 12(2):R63.
- Becker MA, Schumacher HR Jr, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med*. 2005; 353(23): 2450-61.
- Behr TM, Wang X, Aiyar N, et al. Monocyte chemoattractant protein-1 is upregulated in rats with volume-overload congestive heart failure. *Circulation*. 2000; 102(11): 1315-22.
- Bloch C, Hermann G, Yu TF. A radiologic reevaluation of gout: a study of 2,000 patients. *AJR Am J Roentgenol* 1980; 134(4):781-7.
- Bose B, Badve SV, Hiremath SS, et al. Effects of uric acid-lowering therapy on renal outcomes: a systematic review and meta-analysis. *Nephrol Dial Transplant*. 2014; 29(2):406-13.
- Braun WE, Richmond BJ, Protiva DA, et al. The incidence and management of osteoporosis, gout, and avascular necrosis in recipients of renal allografts functioning more than 20 years treated with prednisone and azathioprine. *Transplant Proc*. 1999; 31:1366-9.
- Burnier M, Rutschmann B, Nussberger J, et al. Salt-dependent renal effects of an angiotensin II antagonist in healthy subjects. *Hypertension*. 1993; 22(3):339-47.
- Burns CM, Wortmann RL. Gout therapeutics: New drugs for an old disease. *Lancet*. 2011; 377:165-77.
- Butler R, Morris AD, Belch JJJ, et al. Allopurinol normalizes endothelial dysfunction in type 2 diabetics with mild hypertension. *Hypertension*. 2000; 35:746-51.
- Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. *N Engl J Med*. 1985; 313:1369-75.
- Campion EW, Glynn RJ, Delabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *Am J Med* 1987; 82(3):421-6.
- Cappola TP, Kass DA, Nelson GS, et al. Allopurinol improves myocardial efficiency in patients with idiopathic dilated cardiomyopathy. *Circulation*. 2001; 104:2407-11.
- Cattermole GN, Man CY, Cheng CH, et al. Oral prednisolone is more cost-effective than oral indomethacin for treating patients with acute gout-like arthritis. *Eur J Emerg Med* 2009; 16(5):261-6.
- Chandrate P, Roddy E, Clarson L, et al. Health related quality of life in gout: a systematic review. *Rheumatology (Oxf)*. 2013; 52(11): 2031-2040.
- Chen H, Mosley TH, Alonso A, et al. Plasma urate and Parkinson's disease in the Atherosclerosis Risk in Communities (ARIC) study. *Am J Epidemiol* 2009; 169:1064-9. doi:10.1093/aje/kwp033.
- Chen K, Fields T, Mancuso CA, et al. Anakinra's efficacy is variable in refractory gout: report of ten cases. *Semin Arthritis Rheum* 2010; 40:210-14. doi:10.1016/j.semarthrit.2010.03.001.
- Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. *Curr Opin Rheumatol* 2010; 22:165-72.
- Choi JWW, Ford ES, Gao X, Choi HK. Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum*. 2008; 59(1):109-16.
- Choi HK, Gao X, Curhan G. Vitamin C intake and the risk of gout in men: a prospective study. *Arch Intern Med*. 2009; 169(5):502-7.
- Cingolani HE, Plastino JA, Escudero EM, et al. The effect of xanthine oxidase inhibition upon ejection fraction in

- heart failure patients: La Plata Study. *J Card Fail.* 2006; 12(7):491-8.
30. Clive DM, Stoff JS. Renal syndromes associated with non-steroidal anti-inflammatory drugs. *N Engl J Med.* 1984; 310(9): 563-72.
 31. Coghlan JG, Flitter WD, Clutton SM, et al. Allopurinol pre-treatment improves postoperative recovery and reduces lipid peroxidation in patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 1994; 107:248-56.
 32. Colcrys full prescribing information. 2009. www.colcrys.com
 33. Dahlöf B. Regression of the ventricular hypertrophy – are there differences between antihypertensive agents? *Cardiology.* 1992; 81(4-5):307-15.
 34. Dalbeth N, Stamp L. Hyperuricemia and gout: time for a new staging system? *Ann Rheum Dis.* 2014; 0:1-3. doi:10.1136/annrheumdis-2014-205304.
 35. Decker JL. Report from the subcommittee on diagnostic criteria for gout. In: Bennett PH, Wood PH, editors. *Proceedings from the Third International Symposium*; 1966 June 5-10; New York, New York. Amsterdam: Excerpta Medica Foundation; 1968:385-7.
 36. Diaz-Torné C, Perez-Herrero N, Perez-Ruiz F. New medications in development for the treatment of hyperuricemia of gout. *Curr Opin Rheumatol* 2015; 27:164-9. doi:10.1097/BOR.0000000000000146.
 37. Dinnel J, Moore BL, Skiver BM, Bose P. Rasburicase in the management of tumor lysis: an evidence-based review of its place in therapy. *Cor Evid.* 2015; 10:23-38.
 38. Doehner W, Schoene N, Rauchhaus M, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. *Circulation.* 2002; 105:2619-24.
 39. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology / American Heart Association Task Force on Practice Guidelines. *Circulation.* 2014 Jan 24. 129 (25 Suppl 2):S76-99.
 40. Edwards NL, So A. Emerging therapies for gout. *Rheum Dis Clin North Am* 2014; 40:375-87. doi:10.1016/j.rdc.2014.01.01.
 41. El-Menyar AA. Cytokines and myocardial dysfunction: state of the art. *J Card Fail.* 2008; 14:61-74.
 42. Enomoto A, Endou H. Roles of organic anion transporters (OATs) and a urate transporter (URAT1) in the pathophysiology of human disease. *Clin Exp Nephrol* 2005; 9:195-205.
 43. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality The NHANES I Epidemiologic Follow-Up Study, 1971-1992. *National Health and Nutrition Examination Survey. JAMA* 2000; 283(18):2404-10.
 44. Farquharson CA, Butler R, Hill A, et al. Allopurinol improves endothelial dysfunction in chronic heart failure. *Circulation.* 2002; 106:221-6.
 45. Fauvel JP, Velon S, Berra N, et al. Effects of losartan on renal function in patients with essential hypertension. *J Cardiovasc Pharmacol.* 1996; 28:259-63.
 46. Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. The Committee on Outcome Measures in Rheumatoid Arthritis Clinical Trials. *Arthritis Rheum.* 1993; 36(6):729-40.
 47. Fernandez C, Noguera R, Ganzalez JA, Pascual E. Treatment of acute attacks of gout with a small dose of intra-articular triamcinolone acetonide [letter]. *J Rheumatol* 1999; 26(10):2285-6.
 48. Filippucci E, Di Geso L, Grassi W. Tips and tricks to recognize microcrystalline arthritis. *Rheumatology (Oxf).* 2012; 51(7):vii18-21.
 49. Flower RJ, Moncada S, Vane JR. Analgesic-antipyretics and anti-inflammatory agents: Drugs employed in the treatment of gout. In: *The Pharmacologic Basis of Therapeutics*, 7th Ed., edited by Gilman AG, Goodman LS, Rall TW, Murad F, New York, Macmillan, 1985, pp 674-715.
 50. Franse LV, Pahor M, Di Bari M, et al. Serum uric acid, diuretic treatment and risk of cardiovascular events in the Systolic Hypertension in the Elderly Program (SHEP). *J Hypertens.* 2000; 18:1149-54.
 51. Gavin AD, Struthers AD. Allopurinol reduces B-type natriuretic peptide concentrations and haemoglobin but does not alter exercise capacity in chronic heart failure. *Heart.* 2005; 91:749-53.
 52. George J, Carr E, Davies J, et al. High-dose allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering uric acid. *Circulation.* 2006; 114(23):2508-16.
 53. Ghosh P, Cho M, Rawat G, et al. Treatment of acute gouty arthritis in complex hospitalized patients with anakinra. *Arthritis Care Res (Hoboken)* 2013; 65:1381-4.
 54. Givertz MM, Anstrom KJ, Redfield MM, et al. Effects of xanthine oxidase inhibition in hyperuricemic heart failure patients. The xanthine oxidase inhibition for hyperuricemic heart failure patients (EXACT-HF) study. *Circulation.* 2015; 131(20):1763-71.
 55. Glazebrook KN, Guimaraes LS, Murthy NS, et al. Identification of intraarticular and periarticular uric acid crystals with dual-energy CT: initial evaluation. *Radiology.* 2011; 261(2):516-24.
 56. Goicoechea M, Garcia de Vinuesa S, Verdalles U, et al. Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. *CJASN.* 2010; 5(8):1388-93.
 57. Goldfarb E, Smythe CJ. Effects of allopurinol, a xanthine oxidase inhibitor, and sulfinpyrazone upon the urinary and serum urate concentrations in eight patients with tophaceous gout. *Arthritis Rheumatism* 1967; 9(3):414-23.
 58. Gonzales-Ortiz M, Mora-Martinez JM, Martinez-Abundis E, et al. Effect of valsartan on renal handling of uric acid in healthy subjects. *J Nephrol.* 2000; 13:125-7.
 59. Hak AE, Curhan GC, Grodstein F, et al. Menopause, postmenopausal hormone use and risk of incident gout. *Ann Rheum Dis* 2010; 69:1305-9.
 60. Hara M, Sakata Y, Nakatani D, et al. Osaka Acute Coronary Insufficiency Study (OACIS) Investigators. Low levels of serum n-3 polyunsaturated fatty acids are associated with worse heart failure-free survival in patients after acute myocardial infarction. *Circ J.* 2013; 77:153-62.

61. Hare JM, Mangal B, Brown J, et al. Impact of oxypurinol in patients with symptomatic heart failure. Results of the OPT-CHF study. *J Am Coll Cardiol*. 2008; 51:2301-9.
62. Harris KP, Jenkins D, Walls J. Non-steroidal anti-inflammatory drugs and cyclosporine: a potentially serious adverse interaction. *Transplantation*. 1988; 46:598-9.
63. Harrold LR, Mazor KM, Negron A, et al. Primary care providers' knowledge, beliefs and treatment practices for gout: results of a physician questionnaire. *Rheumatology (Oxf)*. 2013; 52(9):1623-9.
64. Hatch M, Freel RW, Shahinfar S, et al. Effects of the specific angiotensin II receptor antagonist losartan on urate homeostasis and intestinal urate transport. *J Pharmacol Exp Ther*. 1996; 276:187-93.
65. Hill EM, Sky K, Sit M, et al. Does starting allopurinol prolong acute treated gout? A randomized clinical trial. *J Clin Rheumatol* 2015; 21:120-5.
66. Hirsch GA, Bottomley PA, Gerstenblith G, et al. Allopurinol acutely increases adenosine triphosphate energy delivery in failing human hearts. *J Am Coll Cardiol*. 2012; 59(9):802-8.
67. Hirsch J, Terkeltaub R, Khanna D, et al. Gout disease specific quality of life and the association with gout characteristics. *Patient Relat Outcome Meas*. 2010; 1:1-8.
68. Hou M, Hu Q, Chen Y, et al. Acute effects of febuxostat, a nonpurine selective inhibitor of xanthine oxidase, in pacing induced heart failure. *J Cardiovasc Pharmacol*. 2006; 5:255-63.
69. Huang HY, Appel LJ, Choi MJ, et al. The effects of vitamin C supplementation on serum concentrations of uric acid: results of a randomized controlled trial. *Arthritis Rheum*. 2005; 52:1843-7.
70. Ito O, Hasegawa Y, Sato K, et al. A case of exercise-induced acute renal failure in a patient with idiopathic renal hypouricemia developed during antihypertensive therapy with losartan and trichlormethiazide. *Hypertens Res*. 2003; 26:509-13.
71. Jacobs F, Mamzer-Bruneel MF, Skhiri H, et al. Safety of the mycophenolate mofetil-allopurinol combination in kidney transplant recipients with gout. *Transplantation*. 1997; 64:1087-18.
72. Jagose JT, Bailey RR. Muscle weakness due to colchicine in a renal transplant recipient. *N Med J*. 1997; 110:343.
73. Janssens HJ, Fransen J, van de Lisdonk EH, et al. A diagnostic rule for acute gouty arthritis in primary care without joint fluid analysis. *Arch Intern Med*. 2010; 170:1120-6.
74. Janssens HJ, Janssen M, van de Lisdonk EH, et al. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. *Lancet* 2008; 371:1854-60.
75. Jenkinson C, Coulter A, Wright L. Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ*. 1993; 306(6890):1437-40.
76. Juge PA, Truchetet ME, Pillebout E, et al. Efficacy and safety of febuxostat in 73 gouty patients with stage 4/5 chronic kidney disease: result from a retrospective 9 multicenter study. *Ann Rheum Dis*. 2016; 75(2):382.
77. Kamper AL, Nielsen AH. Uricosuric effect of losartan in patients with renal transplants. *Transplantation*. 2001; 72:671-4.
78. Karachalios GN, Donas G. Sulindac in the treatment of acute gout arthritis. *Int J Tissue React* 1982; 4:297-9.
79. Kellgren JH, Jeffrey MR, Ball J. The epidemiology of chronic rheumatism. Vol. I. Oxford: Blackwell Scientific. 1963; p. 326-7.
80. Khanna D., Fitzgerald J., Khanna P. et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res*. 2012; 64:1431-46.
81. Khanna D., Khanna P., Fitzgerald J. et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: Therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res*. 2012; 64:1447-61.
82. Khanna PP, Perez-Ruiz F, Maranian P, et al. Long-term therapy for chronic gout results in clinically important improvements in the health-related quality of life: short form-36 is responsive to change in chronic gout. *Rheumatology (Oxf)*. 2011; 50(4):740-5.
83. Khitan Z, Kim DH. Fructose: a key factor in the development of metabolic syndrome and hypertension. *J Nutr Metab*. 2013;682673.
84. Kim KM, Kim SS, Yun S, et al. Uric acid contributes to glomerular filtration rate deterioration in renal transplantation. *Nephron Clin Pract*. 2011; 118:136-42.
85. Kim SM, Choi YW, Seok HY, et al. Reducing Serum Uric Acid Attenuates TGF-beta (1)-Induced Profibrogenic Progression in Type 2 Diabetic Nephropathy. *Nephron Experimental nephrology*. 2013; 121:e108-e120.
86. Kim TS, Pae CU, Yoon SJ, et al. Decreased plasma antioxidants in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 2006; 21:344-8. doi:10.1002/gps.1469.
87. Kramer HM, Curhan G. The association between gout and nephrolithiasis: the National Health and Nutrition Examination Survey III, 1988-1994. *Am J Kidney Dis* 2002;40:37-42.
88. Leary WP, Reyes AJ. Angiotensin I converting enzyme inhibitors and the renal excretion of urate. *Cardiovasc Drugs Ther*. 1987; 1(1):29-38.
89. Lee SJ, Hirsch JD, Terkeltaub R, et al. Perceptions of disease and health-related quality of life among patients with gout. *Rheumatology (Oxf)*. 2009; 48(5):582-6.
90. Li C, Hsieh MC, Chang SJ. Metabolic syndrome, diabetes, and hyperuricemia. *Curr Opin Rheumatol*. 2013; 25(2):210-16.
91. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet*. 2001; 357:505-8.
92. Maccagno A, Di Giorgio E, Romanowicz A. Effectiveness of etodolac ('Lodine') compared with naproxen in patients with acute gout. *Curr Med Res Opin* 1991; 12:423-9.
93. Malheiro J, Almeida M, Fonseca I, et al. Hyperuricemia in adult renal allograft recipients: prevalence and predictors. *Transplant Proc*. 2012; 44(8):2369-72.
94. Martinon F. Mechanisms of uric acid crystal-mediated autoinflammation. *Immunol Rev* 2010; 233(1):218-32.
95. Miao Y, Ottenbros SA, Laverman GD, et al. Effect of a reduction in uric acid on renal outcomes during losartan treatment: a post hoc analysis of the reduction of endpoints in non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan Trial. *Hypertension*. 2011; 58:2-7.

96. Mikuls TR, Farrar JT, Bilker WB, Fernandes S, Schumacher HR, Saag KG. Gout epidemiology: results from the UK General Practice Research Database, 1990–1999. *Ann Rheum Dis* 2005; 64(2):267-72.
97. Milionis HJ, Kakafika AI, Tsouli SG, et al. Effects of statin treatment on uric acid homeostasis in patients with primary hyperlipidemia. *Am Heart J* 2004; 148(4):635-40.
98. Moriwaki Y, Yamamoto T, Takahashi S, Yamakita J, Tsutsumi Z, Hada T. Spot urine uric acid to creatinine ratio used in the estimation of uric acid excretion in primary gout [see comment]. *J Rheumatol* 2001; 28 (6):1306-10.
99. Nakagawa T, Hu H, Zharikov S, et al. A causal role for uric acid in fructose-induced metabolic syndrome. *Am J Physiol Renal Physiol*. 2006; 290:F625-F631.
100. Nakagomi A, Saiki Y, Noma S, et al. Effects of febuxostat and allopurinol on the inflammation and cardiac function in chronic heart failure patients with hyperuricemia. *IJC Metabolic and Endocrine*. 2015; 8:46-55.
101. Nakashima M, Uematsu T, Kosuge K, et al. Pilot study of the uricosuric effect of DuP-753, a new angiotensin II receptor antagonist, in healthy subjects. *Eur J Clin Pharmacol*. 1992; 42:333-5.
102. Naredo E, Uson J, Jimenez-Palop M, et al. Ultrasound-detected musculoskeletal urate crystal deposition: which joints and what findings should be assessed for diagnosing gout? *Ann Rheum Dis* 2014; 73:1522-8.
103. Naumova AV, Chacko VP, Ouwerkerk R, et al. Xanthine oxidase inhibitors improve energetics and function after infarction in failing mouse hearts. *Am J Physiol Heart Circ Physiol*. 2006; 290: H837-H843.
104. Neogi T, Hunter D J, Chasson C E, Cunningham J A, Zhang Y Q. Frequency of inappropriate management of acute gout attacks. *Arthritis Rheum* 2004. 50 (9 suppl) S339.
105. Neogi T, Jansen T, Dalbeth N, et al. 2015 Gout Classification Criteria. An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. *Arthritis and Rheumatology*. 2015; 67(10) 2557-68.
106. Noguchi Y, Tatsuno I, Suyama K, et al. Effect of fenofibrate on uric acid metabolism in Japanese hyperlipidemic patients. *J Atheroscler Thromb*. 2004; 11(6):335-40.
107. Nomura J, Busso N, Ives A, et al. Febuxostat, an inhibitor of xanthine oxidase, suppresses lipopolysaccharide-induced MCP-1 production via MAPK phosphatase-1-mediated inactivation of JNK. *PLoS ONE*. 2013; 8(9): e75527.
108. Ogata N, Fujimori S, Oka Y, et al. Effects of three strong statins (atorvastatin, pitavastatin, and rosuvastatin) on serum uric acid levels in dyslipidemic patients. *Nucleosides Nucleotides Nucleic Acids*. 2010; 29(4-6): 321-4.
109. Ogino K, Kato M, Furuse Y, et al. Uric acid lowering treatment with benzbromarone in patients with heart failure: a double-blind placebo-controlled crossover preliminary study. *Circ Heart Fail*. 2010; 3(1):73-81.
110. Ottaviani S, Moltó A, Ea HK, et al. Efficacy of anakinra in gouty arthritis: a retrospective study of 40 cases. *Arthritis Res Ther* 2013; 15:R123. doi:10.1186/ar4303CrossRefPubMedGoogle Scholar
111. Pak CY, Poindexter JR, Peterson RD, et al. Biochemical distinction between hyperuricosuric calcium urolithiasis and gouty diathesis. *Urology* 2002; 60:789-94.
112. Pal B, Foxall M, Dysart T, et al. How is gout managed in primary care? A review of current practice and proposed guidelines. *Clin Rheumatol*. 2000; 19(1):21-5.
113. Palmer BF. Renal complications associated with use of nonsteroidal anti-inflammatory agents. *J Invest Med*. 1995; 43:516-33.
114. Pelaez-Ballestas I, Hernandez Cuevas C, Burgos-Vargas R, et al. Diagnosis of chronic gout: evaluating the American College of Rheumatology proposal, European League Against Rheumatism recommendations, and clinical judgement. *J Rheumatol*. 2010; 37:1743-8.
115. Perez Ruiz F, Calabozo M, Pijoan JI, et al. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum* 2002; 47(4):356-60.
116. Perez-Ruiz F, Herrero-Beites AM, Carmona L. A two-stage approach to the treatment of hyperuricemia in gout: the “dirty dish” hypothesis. *Arthritis Rheum* 2011; 63:4002-6. doi:10.1002/art.30649.
117. Perez-Ruiz F, Herrero-Beites AM. Evaluation and treatment of gout as a chronic disease. *Adv Ther*. 2012; 29(11):935-46.
118. Perez-Ruiz F, Sundry JS, Miner JN, Cravets M, Storgard C, RDEA594-203 Study Group. Lesinurad in combination with allopurinol: results of a phase 2 randomised double-blind study in patients with gout with an inadequate response to allopurinol. *Ann Rheum Dis*. 2016; 7(6):433-42.
119. Perez-Ruiz F, Sundry JS, Miner JN, et al. Lesinurad in combination with allopurinol: results of a phase 2, randomised, double-blind study in patients with gout with an inadequate response to allopurinol. *Ann Rheum Dis* 2016; 75:1074-80.
120. Perez-Ruiz F, Ullate PG, Amenabar JJ, et al. Long-term efficacy of hyperuricemia treatment in renal transplant patients. *Nephrol Dial Transplant* 2003; 18(3):603-6.
121. Perez-Ruiz F, Gomez-Ullate P, Amenabar JJ, et al. Long-term efficacy of hyperuricemia treatment in renal transplant patients. *Nephrol Dial Transplant* 2003; 18:603-6.
122. Pui K, Gow PJ, Dalbeth N. Efficacy and tolerability of probenecid as urate-lowering therapy in gout; clinical experience in high-prevalence population. *J Rheumatol* 2013; 40:872-6. doi:10.3899/jrheum.121301.
123. Puig JG, Martinez MA. Hyperuricemia, gout and the metabolic syndrome. *Curr Opin Rheumatol*. 2008; 20(2): 187-91.
124. Puig JG, Mateos F, Buno A, et al. Effect of eprosartan and losartan on uric acid metabolism in patients with essential hypertension. *J Hypertens*. 1999; 17(7):1033-9.
125. Puig JG, De Miguel E, Castillo MC, et al. Asymptomatic hyperuricemia: impact of ultrasonography. *Nucleosides Nucleotides Nucl Acids* 2008; 27(6):592-5.
126. Rainer TH, Cheng CH, Janssens HJ, et al. Oral prednisolone in the treatment of acute gout: a pragmatic, multicenter, double-blind, randomized trial. *Ann Intern Med* 2016; 164(7):464:71.
127. Rees F, Jenkins W, Doherty M. Patients with gout adhere to curative treatment if informed appropriately: proof-of-concept observational study. *Ann Rheum Dis* 2013; 72:826-30.
128. Reinders MK, van Roon EN, Houtman PM, et al. Biochemical effectiveness of allopurinol and allopurinol-probenecid in

- previously benzbromarone-treated gout patients. *Clin Rheumatol* 2007; 26(9):1459-65.
129. Rigby A S, Wood P H. Serum uric acid levels and gout: what does this herald for the population? *Clin Exp Rheumatol* 1994; 12(4):395-400.
 130. Roch-Ramel F, Guisan B, Diezi J. Effects of uricosuric and antiuricosuric agents on urate transport in human brush-border membrane vesicles. *J Pharmacol Exp Ther* 1997; 280(2):839-45.
 131. Roddy E, Zhang W, Doherty M. Is gout associated with reduced quality of life? A case-control study. *Rheumatology (Oxf)* 2007; 46:1441-4.
 132. Rubin BR, Burton R, Navarra S, et al. Efficacy and safety profile of treatment with etoricoxib 120 mg once daily compared with indomethacin 50 mg three times daily in acute gout: a randomized controlled trial. *Arthritis Rheum* 2004; 50:598-606.
 133. Ruilope LM, Kirwan BA, de Brouwer S, et al. Uric acid and other renal function parameters in patients with stable angina pectoris participating in the ACTION trial: impact of nifedipine GITS (gastro-intestinal therapeutic system) and relation to outcome. *J Hypertens.* 2007; 25(8):1711-8.
 134. Schlesinger N, Alten RE, Bardin T, et al. Canakinumab for acute gouty arthritis in patients with limited treatment options: results from two randomised, multicentre, active-controlled, double-blind trials and their initial extensions. *Ann Rheum Dis* 2012; 71:1839-48.
 135. Schumacher HR, Chen LX, Zhang LY. Diagnosis of crystal-associated disease: where do we stand? *Bioanalysis* 2011; 3:1081-3.
 136. Schumacher Jr. HR, Becker MA, Wortmann RL, et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum* 2008; 59(11):1540-8.
 137. Sezai A, Soma M, Nakata K, et al. Comparison of febuxostat and allopurinol for hyperuricemia in cardiac surgery patients (NU-FLASH Trial). *Circ J* 2013; 77(8): 2043-9.
 138. Shahinfar S, Simpson RL, Carides AD, et al. Safety of losartan in hypertensive patients with thiazide-induced hyperuricemia. *Kidney Int* 1999; 56(5):1879-85.
 139. Shen X, Li J, Fu Q, et al. Comparison of efficacy and safety between febuxostat and allopurinol in early post-renal transplant recipients with new onset of hyperuricemia. *J Clin Pharm Ther* 2019; 44(2):318-26.
 140. Shi B, Ni Z, Cao L, et al. Serum IL-18 is closely associated with tubulointerstitial injury and predicts renal prognosis in IgA Nephropathy. *Mediators of Inflammation.* 2012; 2012:728417.
 141. Singh J. A, Reddy SG, Kundukulam J. Risk factors for gout and prevention: a systematic review of the literature. *Curr Opin Rheumatol* 2011; 23:192-202.
 142. Siu YP, Leung KT, Tong MK, et al. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis.* 2006; 47(1):51-9.
 143. Sivera F, Andres M. Carmona L, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative, *Ann Rheum Dis* 2014; 73:328-35.
 144. So A. Developments in the scientific and clinical understanding of gout. *Arthritis Res Ther.* 2008; 10:221.
 145. So A, De Meulemeester M, Pikhak A, et al. Canakinumab for the treatment of acute flares in difficult-to-treat gouty arthritis: Results of a multicenter, phase II, dose-ranging study. *Arthritis Rheum* 2010; 62(10):3064-76.
 146. So A, De Smedt T, Revaz S, Tschopp J. A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res Ther* 2007;9(2):R28.
 147. Sofue T, Inui M, Hara T, et al. Efficacy and safety of febuxostat in the treatment of hyperuricemia in stable kidney transplant recipients. *Drug Des Devel Ther.* 2014; 8:245-53.
 148. Stamp LK, O'Donnell JL, Frampton C, et al. Clinically insignificant effect of supplemental vitamin C on serum urate in patients with gout: a pilot randomized controlled trial. *Arthritis Rheum.* 2013; 65(6):1636-42.
 149. Stamp LK, O'Donnell JL, Zhang M, James J, Frampton C, Barclay ML, et al. Using allopurinol above the dose based on creatinine clearance is effective and safe in patients with chronic gout, including those with renal impairment. *Arthritis Rheum* 2011; 63:412-21.
 150. Stamp LK, Taylor WJ, Jones PB, et al. Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. *Arthritis Rheum* 2012; 64:2529-36. doi:10.1002/art.34488.
 151. Stein HB, Hasan A, Fox IH. Ascorbic acid-induced uricosuria. A consequence of megavitamin therapy. *Ann Intern Med* 1976; 84:385-8.
 152. Stocker SL, Graham GG, McLachlan AJ, et al. Pharmacokinetic and pharmacodynamic interaction between allopurinol and probenecid in patients with gout. *J Rheumatol* 2011; 38:904-10.
 153. Struthers AD, Donnan PT, Lindsay P, et al. Effect of allopurinol on mortality and hospitalisations in chronic heart failure: a retrospective cohort study. *Heart.* 2002; 87:229-34.
 154. Stull LB, Leppo MK, Szweda L, et al. Chronic treatment with allopurinol boosts survival and cardiac contractility in murine postischemic cardiomyopathy. *Circ. Res.* 2004; 95(10):1005-1.
 155. Sturge RA, Scott JT, Hamilton EB, et al. Multicentre trial of naproxen and phenylbutazone in acute gout. *Ann Rheum Dis* 1977; 36(1):80-2.
 156. Sugino H, Shimada H. Intravenous infusion of diltiazem causes uricosuria with concomitant hypouricemia in rats. *Biol Pharm Bull.* 1996; 19:627-9.
 157. Sulfipyrazone in the prevention of cardiac death after myocardial infarction. The Anturane Reinfarction Trial. *N Engl J Med* 1978; 298:289-95.
 158. Sundry JS, Baraf HS, Yood RA, et al. Efficacy and tolerability of pegloticase for the treatment of chronic gout in patients refractory to conventional treatment: two randomized controlled trials. *JAMA* 2011; 306 (7):711-20.
 159. Taylor TH, Mecchella JN, Larson RJ, et al. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. *Am J Med* 2012; 125(11):1126-34.e7.

160. Terawaki H, Nakayama M, Miyazawa E, et al. Effect of allopurinol on cardiovascular incidence among hypertensive nephropathy patients: the Gonryo study. *Clin Exp Nephrol* 2013; 17(4):549-53.
161. Terkeltaub RA, Furst DE, Digiacinto JL, et al. Novel evidence-based colchicine dose-reduction algorithm to predict and prevent colchicine toxicity in the presence of cytochrome P450 3A4/P-glycoprotein inhibitors. *Arthritis Rheum* 2011; 63(8):2226-37.
162. Terkeltaub RA, Schumacher HR, Carter JD, et al. Rilonacept in the treatment of acute gouty arthritis: a randomized, controlled clinical trial using indomethacin as the active comparator. *Arthritis Res Ther* 2013; 15:R25.
163. Terkeltaub RA. Colchicine update: 2008. *Semin Arthritis Rheum* 2009;38(6):411-9.
164. Tojimbara T, Nakajima I, Yashima J, et al. Efficacy and safety of febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase for the treatment of hyperuricemia in kidney transplant recipients. *Transplant Proc* 2014; 46(2):511-3.
165. Tykarski A. Uric acid and arterial hypertension. III. Effect of nifedipine on serum uric acid level and its renal excretion in primary arterial hypertension. *Pol Arch Med Wewn* 1992; 86(3):177-82.
166. Wallace SL, Robinson H, Masi AT, et al. Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum* 1977; 20(3):895-900.
167. Wason S, Mount D, Faulkner R. Single-dose, open-label study of the differences in pharmacokinetics of colchicine in subjects with renal impairment, including end-stage renal disease. *Clin Drug Investig* 2014; 34:845-55.
168. Wei L, Fahey T, Struthers AD, et al. Association between allopurinol and mortality in heart failure patients: a long-term follow-up study. *Int J Clin Pract* 2009; 63(9):1327-33.
169. Weisskopf MG, O'Reilly E, Chen H, et al. Plasma urate and risk of Parkinson's disease. *Am J Epidemiol* 2007; 166:561-7. doi:10.1093/aje/kwm127.
170. White WB, Chohan S, Dabholker A, et al. Cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular comorbidities. *Am. Heart J* 2012; 164(1):14-20.
171. Winnard D, Wright C, Taylor WJ, et al. National prevalence of gout derived from administrative health data in Aotearoa New Zealand. *Rheumatology* 2012; 51(5): 901-9.
172. Wortmann RL, Macdonald PA, Hunt B, Jackson RL. Effect of prophylaxis on gout flares after the initiation of uratelowering therapy: analysis of data from three phase III trials. *Clin Ther* 2010; 32(14):2386-97.
173. Xilifu D, Abudula A, Rehemu N, et al. Effect of rosuvastatin on hyperuricemic rats and the protective effect on endothelial dysfunction. *Experimental and therapeutic medicine* 2014; 8(6):1683-8.
174. Xu X, Hu X, Lu Z, et al. Xanthine oxidase inhibition with febuxostat attenuates systolic overload-induced left ventricular hypertrophy and dysfunction in mice. *J Card Fail.* 2008; 14(9):746-53.
175. Yamamoto T, Moriwaki Y, Takahashi S, et al. Effect of fenofibrate on plasma concentration and urinary excretion of purine bases and oxypurinol. *J Rheumatol.* 2001; 28:2294-7.
176. Yamamoto Y, Ogino K, Igawa G, et al. Allopurinol reduces neointimal hyperplasia in the carotid artery ligation model in spontaneously hypertensive rats. *Hypertens Res.* 2006; 29:915-21.
177. Yu TF, Berger L, Gutman AB. Renal function in gout. II. Effect of uric acid loading on renal excretion of uric acid. *Am J Med* 1962; 33:829-44.
178. Yu TF, Gutman AB. Paradoxical retention of uric acid by uricosuric drug in low dosage. *Proc Soc Exp Biol Med* 1955; 90:542-7.
179. Zhang Y, Woods R, Chaisson CE, et al. Alcohol consumption as a trigger of recurrent gout attacks. *Am J Med* 2006; 119(9):800.e13-8.
180. Zhu Y., Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. *Arthritis Rheum* 2011; 63:3136-41.
181. Иванова М, Стоилов Р, Манолова И. Анкилозираещ спондилит. София, Таурис Адвертайзинг, 2013.