REVIEW ARTICLE

Gout—Current Diagnosis and Treatment

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SUMMARY

Background: Because of the changing dietary habits of an aging population, hyperuricemia is frequently found in combination with other metabolic disorders. Longstanding elevation of the serum uric acid level can lead to the deposition of monosodium urate crystals, causing gout (arthritis, urate nephropathy, tophi). In Germany, the prevalence of gouty arthritis is estimated at 1.4%, higher than that of rheumatoid arthritis. There are no German guidelines to date for the treatment of gout. Its current treatment is based largely on expert opinion.

Methods: Selective literature review on the diagnosis and treatment of gout.

Results and conclusions: Asymptomatic hyperuricemia is generally not an indication for pharmacological intervention to lower the uric acid level. When gout is clinically manifest, however, acute treatment of gouty arthritis should be followed by determination of the cause of hyperuricemia, and long-term treatment to lower the uric acid level is usually necessary. The goal of treatment is to diminish the body's stores of uric acid crystal deposits (the intrinsic uric acid pool) and thereby to prevent the inflammatory processes that they cause, which lead to structural alterations. In the long term, serum uric acid levels should be kept below 360 µmol/L (6 mg/dL). The available medications for this purpose are allopurinol and various uricosuric agents, e.g., benzbromarone. There is good evidence to support the treatment of gouty attacks by the timely, short-term use of non-steroidal anti-inflammatory drugs (NSAID), colchicine, and glucocorticosteroids.

Key words: allopurinol, gout, hyperuricemia, deposits of uric acid, treatment

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G out, a result of hyperuricemia above 390 µmol/L (6.5 mg/dL), is often associated with other metabolic disorders such as obesity, diabetes mellitus, and hypertonia, and carries an increased risk of cardiovascular problems (1–3, e1). Because of changing dietary and other lifestyle habits, at least 1% to 2% of all adults in the industrialized nations are now affected by gout. In the Framingham Study, 9.2% of men and 0.4% of women had hyperuricemia, and 19% of these suffered from gout (e2).

Gout is the name given to the condition when an excess of uric acid (urate) in the body (hyperuricemia) leads to the formation in various tissues of crystals of monosodium urate. The result is attacks of gout, urate nephropathy, and/or tophi. Apart from hereditary disorders of uric acid excretion and purine metabolism, the main causes of gout are purine-rich food, alcohol consumption, and overweight (4, 5, e3). The incidence of gout correlates strongly with serum urate concentrations, increasing markedly when these exceed 480 µmol/L (8.0 mg/dL) (3, e4).

According to recent studies, gouty arthritis (as an indicator of gout) is the most common form of arthritis seen in general practice in adults, with a prevalence of about 1.4%; this figure rises markedly with age. In comparison, the prevalence of rheumatoid arthritis is about 0.5% to 1% (1, 2, 6). The causes of the observed rising lifetime prevalence of gout are not only increasing life expectancy with the accompanying increase in co-morbid conditions such as kidney failure, but also the consumption of drugs that inhibit uric acid excretion, e.g. thiazide (e5–e7).

Compared with women, men have a four- to ninefold increased risk of developing gout. Women often do not develop gout until they reach menopause, when the uricosuric action of estrogens is lost. As a rule, in Germany gout is treated primarily by primary care physicians and internists. Patients with persistent disease, those with an atypical course with polyarticular gout or joint destruction, or those whose cases are complicated by progressive kidney failure or allopurinol intolerance are treated by rheumatologists or nephrologists (2).

Unfortunately no guidelines exist in Germany for the diagnosis and treatment of gout; all that have been published are recommendations on the basis of experience and expert opinion (7). European recommendations for the management of gout were published in 2006 by

TABLE 1

Long-term medical treatment to reduce uric acid. Evidence levels (EL) are shown in parentheses

Active substance/dosages (evidence level)	Comments/concerns
Allopurinol 100–300 mg/d (short-term up to max. 600–800 mg/d) (EL Ib)	Renal function (dose reduction) Drug interactions (metabolization of azathioprine and 6-mercaptopurine is inhibited, leading to serious neutropenia) Target serum uric acid levels are not always achieved Hypersensitivity reactions in 1 case in 300 (very rarely fatal; often start after latent period of weeks or months) Nonselective inhibition of xanthine oxidase
Benzbromarone 20–100 mg/d (EL Ib)	Liver toxicity Risk of uric acid stone formation
Probenecid 1–3 g/d as separate doses (EL Ib)	Only when renal function is normal Drug interactions Target serum uric acid levels are not always achieved Requirement: several doses must be spread throughout the day
Urinary alkalizing substances (citrate) Blemaren 3 × 1–2 dispersible tablets (EL III)	Check urinary pH every 2 hours; uric acid excretion is improved at low urinary pH. To prevent kidney stones, take 3–4 times daily alongside treatment with uricosuric drugs. Costs often not reimbursed

the European League Against Rheumatism (EULAR), and the British Society for Rheumatology (BSR) published its guidelines in 2007 (8, 9). Each of these was produced by a professional rheumatological body and was based on a comprehensive analysis of the evidence base as represented by the current international literature. Although they may be regarded as high-quality guidelines, because other specialities involved in the treatment of gout, such as general medicine, were not involved in their production, they cannot by definition be equated with S3 guidelines.

On the basis of these publications, an additional PubMed literature search was carried out using the earch terms "gout" and "randomised trial" and covering the dates from 1980 to the first quarter of 2008. This resulted in the identification of a further 14 randomized, controlled studies of treatment and its results which were included in the present article. This review article aims to shed light on the subject of the diagnosis and treatment of gout and present guidelines for medical practice with defined levels of evidence (EL) *(Tables 1, 2).*

Pathophysiology and clinical features of gout
Urate is the end product of purine metabolism. Important steps in this are the degradation of xanthine and hypoxanthine by the enzyme xanthine oxidase. Urate is excreted primarily via the kidneys. In recent years important urate transport proteins such as the human URAT1 transporter (hURAT1) and the fructose transporter SCL2A9 have been characterized (10, 11). Polymorphisms in the corresponding genes lead to a disturbance in the function of the transporters, with reduced renal urate excretion and consequent accumulation of urate, and are often associated with gout (12, e8, e9). The transport function is also affected by various

drugs: for example, low-dose aspirin treatment and diuretics reduce urate excretion by inhibiting hURAT1 (10). In practice, these conditions in which the excretion of urate is reduced can be distinguished from other, rarer causes of hyperuricemia in which the production of urate is increased, e.g., in hematological diseases with increased cell turnover *(Table 3).*

In accordance with physicochemical laws, once uric acid has passed its saturation point of 400 µmol/L (6.8 mg/dL; at 37 °C, pH 7.4), it starts to precipitate out in the form of monosodium urate crystals (13). Sites of predilection are peripheral regions of the body (e.g., the joints of the extremities) when ambient temperatures are low and inflamed joints (14) *(Figure 1).* Urate crystals lead to activation of the NALP3 inflammasome with release of proinflammatory cytokines, among them interleukins 1, 18, and 8, and of tumor necrosis factor, attracting more polymorphonuclear neutrophilic granulocytes (e10–e12).

The usual triggers of gout attacks are a sudden rise in serum urate, e.g., after excessive eating and alcohol intake (4, 5). A rapid drop in serum urate, as for example at the start of urate-lowering therapy, can also trigger an attack of gout. In this case the release of urate from the margins of crystal deposits as a result of the concentration gradient between serum and tissue seems to stimulate an immune response (15, e13). The typical first manifestation of gout is an acute episode of monoarticular arthritis at the metatarsophalangeal joint of the large toe (podagra) that is very painful, starts at night, lasts around a week, and in many cases is self-limiting (e14) *(Figure 1).*

The deposition of urate crystals in various tissues such as joints, connective tissue, and kidneys explains the chronic character of the gout. Almost 90% of patients who have suffered an attack of gout experience repeat

episodes during the following 5 years (16). In the course of the disease atypical manifestations may be seen: other joints (e.g., finger joints) may be affected, and oligo-articular or polyarticular arthritis may develop *(Figure 2)*. The differential diagnosis includes other crystal-induced forms of arthritis such as pseudogout/chondro-calcinosis with deposition of calcium pyrophosphate dihydrate crystals, and oxalosis arthropathies (e.g., secondary calcium oxalate deposits in patients on long-term dialysis). In addition, septic arthritis, psoriatic arthritis, and hemochromatosis should be ruled out (17).

Diagnosing gout

A suspected diagnosis of gout may safely be made on the basis of an episode of excessive eating and/or drink-ing (of alcohol) in the recent history—e.g., a barbecue—when the large toe shows the typical signs of a gout attack and the serum concentration of urate is raised. It is quite common for the serum urate level to be normal or low during an attack, so the best time to measure it is 2 to 3 weeks after an attack (evidence level [EL] IV) (15, 18, 19). If the manifestation is atypical and serum urate normal, joint puncture to demonstrate the presence of crystals is highly desirable (EL IIb); the differential diagnosis in such a case includes septic arthritis (8, 20). The important thing here is to examine the untreated crystals (urate crystals dissolve in formalin) under a polarization microscope. The crystals appear as bire-fringent intra- and extracellular needles 10 to 20 μm in length.

Once gout has been diagnosed, the possible causes need to be identified. Since, given the appropriate genetic predisposition, it is possible that, in addition to the in-creased urate (often promoted by diet), cell turnover may in rare cases be increased due to the presence of occult neoplastic disease (e.g., leukemia or plasma-cytosis), cell count, differential cell count, and erythrocyte sedimentation rate should be carried out, to-gether with determination of lactate dehydrogenase and possibly serum albumin electrophoresis (EL IV) (13, e15).

If no explanation for the gout attack is found, especially in younger patients with a family history of gout, then owing to the frequent association with impaired renal function, serum creatinine should be determined, as should 12- or 24-hour urinary clearance of creatinine and urate, and a urinary pH strip test should be performed (EL IIb) (7, 8, 11) *(Figure 3)*. Since patients with gout have an up to 2.5-times increased risk of developing urate stones, leading to urate nephropathy, the kidneys should be examined by ultrasound to rule out the pres-ence of stones (21, 22). Because of the frequent associa-tion with other metabolic and endocrine diseases—over 50% of patients have a metabolic syndrome—the guide-lines for risk stratification recommend determination of fasting blood sugar, and possibly of HbA_{1c}, fasting blood lipids/cholesterol, and thyroid parameters (EL IIa to IIb) (1, 2, 9).

In the early stages of gouty arthritis, erosive joint changes are only rarely seen on radiographs. Despite

TABLE 2	
Evidence level	
Evidence level	**Underlying evidence/explanation**
Ia	Meta-analysis of randomized controlled studies
Ib	At least one randomized controlled study
IIa	At least one controlled study, without randomization
IIb	At least one experimental study
III	At least one nonexperimental, descriptive study (e.g., comparative or case-control study)
IV	Expert reports and opinions and/or experience of respected authorities

TABLE 3	
Clinical causes of increased urate production and/or reduced urate excretion, modified from (14)	
Causes of increased urate production	
Dietary	Purine-rich and fructose-rich foods, weight loss (fasting)
Hematological	Myeloproliferative and lymphoproliferative diseases
Other	Psoriasis, tumor lysis syndrome
Causes of reduced renal urate excretion	
Drugs	Cyclosporine, thiazides, loop diuretics, aspirin (500–1000 mg/d)
Renal	Hypertension, polycystic kidney disease, chronic renal failure of various etiologies
Metabolic/endocrinological	Dehydration (often associated with surgery), lactic acidosis, ketosis, hypothyroidism
Other	Obesity
Combined mechanisms	
	Alcohol, shock, metabolic syndrome (obesity, hypertriglyceridemia)

this, in case of doubt the affected joints should still undergo x-ray in order to rule out other causes such as osteoarthritis of the big toe MTP joint or psoriatic arthritis (EL IIb) *(Figure 2)* (8). Joint effusions and tophi can be well demonstrated by joint ultrasonography, and this is often helpful before joint puncture or to monitor the course of the disease (EL III) (e16, e17).

Treatment of gout

The first therapeutic goal is acute treatment of the gout attack with rapid alleviation of pain and inhibition of the inflammation. A longer-term goal is to prevent further attacks, eliminate tophi, and prevent joint destruction, by consistently reducing the level of urate (9). It is postulated that gout is "curable" if existing deposits of urate crystals can be successfully removed and the formation of new precipitates prevented (16). To achieve

Figure 1: Acute gout attack with classic podagra and synovitis in the second metacarpophalangeal joint

this, according to international recommendations, serum urate levels in patients with recurring attacks of gout should if possible be kept below 360 µmol/L (6.0 mg/dL) (EL III) (8, 9, e18, e19, e20).

Acute treatment of the gout attack

In addition to nonspecific measures (EN III) such as resting and cooling the affected limb, nonsteroidal anti-inflammatory drugs (NSAIDs) are used (19). The first line of treatment is early, short-term treatment with an NSAID such as diclofenac (up to 250 mg/d) or ibuprofen (up to 2400 mg/d) or indomethacin (up to 150 mg/d), and the cyclooxygenase-2 inhibitor etoricoxib (120 mg/d) (EL Ib) (e21). If the patient has a history of gastrointestinal ulcers or bleeding, proton pump inhibitors should be given in addition (e22). Alternatively, so long as renal function is normal, colchicine may be given; at a dosage of 0.5 mg every 2 hours, this settles the gout attack within 1 day for 80% of patients (e23). However, high doses often lead to nausea and diarrhea. Given up to three times at a dose of 0.5 mg/d, it is usually well tolerated and adequately

effective (EL Ib) (9, 18, e24, e25). As a further option, especially where there are contraindications, intolerance, or advanced kidney failure, glucocorticosteroids (20 to 40 mg prednisolone equivalent/d) may be given (EL Ib) *(Table 4)* (7, 19, e26).

Long-term treatment to lower uric acid levels

As a general measure, the patient should be given advice on possible changes of life habits that could lead to an improvement in his or her overall metabolic profile (19). An extensive interview at the start of therapy often improves the patient's understanding and therefore also the compliance. Many patients fail to understand that the treatment for the acute gout attack is not treatment for the actual cause of the gout. As has been shown recently, in Germany patients often stop taking their urate-lowering medication after 3 months if they have no symptoms; at the end of a year only 30% of gout patients are still receiving allopurinol (2).

In addition to reduced consumption of purine-rich foods such as offal and seafood, patients should also limit their consumption of fructose-containing drinks (i.e., sugar-sweetened soft drinks) as these reduce the excretion of uric acid. The diet should be rich in milk and skimmed milk products and in vegetable protein (4). An important element is limited consumption of alcohol: There should be at least three alcohol-free days a week. Beer should be avoided because of its high purine content, but a glass of wine is regarded as harmless in gout (5). Careful weight loss of less than 1 kg/month with light physical exercise is desirable (e27); more rapid loss of weight could lead to ketoacidosis, provoking gout attacks. Patients with a history of kidney stones are recommended to drink more than 2 L/d. These changes in life habits (EL IIb to IV), however, usually make only a moderate contribution to urate reduction. A consistently purine-poor diet, for example, may be expected to result in a 10% to 15% reduction in serum urate concentration (4). Given that for many gout patients the serum urate concentration measured before the start of treatment is 480 µmol/L (8 mg/dL), such a reduction would result in a value of 400 µmol/L (6.7 mg/dL)—still above the required target range for gout patients (19).

Figure 2:
Chronic gout.
a) Tophaceous gout with destructive joint changes and subcutaneous deposits of uric acid,
b) radiological changes in tophaceous gout

Indications for and timing of additional urate-lowering drug therapy

Although it may be difficult to implement in practice, it is advisable to start patients who have suffered a second attack of gout within a year on a course of drug therapy to increase the excretion of uric acid in the urine. Other indications for urate-lowering drug therapy are destructive joint changes and/or tophi and the presence of gout-related kidney failure (urate nephropathy) with or without uric acid stones (EL IIb to IV) (19, e28, e29).

If at all possible, the treatment should not start during an acute attack, since the dissolution of crystal deposits increases the risk of gout attacks (EL IV) (e30). If possible, it is advisable to provide the patient with NSAIDs during the attack, and to determine urate levels at a follow-up visit 2 to 3 weeks later before starting treatment. The inexpensive xanthine oxidase inhibitor allopurinol has been available for urate-lowering therapy in Germany since 1964 (e31). Allopurinol should be gradually titrated up with the serum urate level being monitored. Treatment starts with 100 mg and depending on the urate value is increased by 50 to 100 mg per week until a maximum of 800 mg is reached (EL III) (19). In a patient with reduced kidney function, the dosage must be matched to the glomerular filtration rate (GFR < 30 mL/min: 100 mg allopurinol every second day) (23). This is important to prevent toxic accumulation of oxipurinol, a long-acting metabolite of allopurinol, and the risk of development of a hypersensitivity to allopurinol (23, e32, e33). Although 2% of patients given allopurinol have an uncomplicated skin reaction (rash and itching), in 1 out of 300 a hypersensitivity reaction can occur which in 20% of cases is fatal (e34). Typical features are generalized itching with eczema-type skin changes, raised liver values, and eosinophilia, which can occur after a latency period of weeks or months after the first administration of allopurinol (24, e33). Patients with allopurinol intolerance, inadequate reduction of urate, and/or primary hyperuricemia with impaired renal excretion of urate (<800 mg/24 h) but otherwise normal renal function, can be treated with the uricosuric drugs benzbromarone (20 to 100 mg/d) or probenecid (1 to 3 g/d in three separate doses); liver values must be monitored. For kidney stone prophylaxis and additional improvement of urate excretion, patients with low urinary pH may be given urine-alkalizing substances (EL Ia to III) (7, e35) (Table 1).

Some interesting results have been recently published from a randomized study comparing the three available substances in relation to their urate-lowering effect, with the target value for serum urate set at below 300 µmol/L (5.0 mg/dL). Among the patients given 300 mg/d allopurinol, only 24% achieved optimal urate reduction; the comparable figures were 92% of those given 200 mg/d benzbromarone and 65% of those given 2000 mg/d probenecid (EL Ib) (e36). If more gout attacks occur during urate-lowering treatment, colchicine (0.5 mg/d) is recommended for the first 6 weeks to 6 months for prophylaxis (EL Ib). In our experience, however, this is very rarely required (7, 9, 19, e37).

FIGURE 3
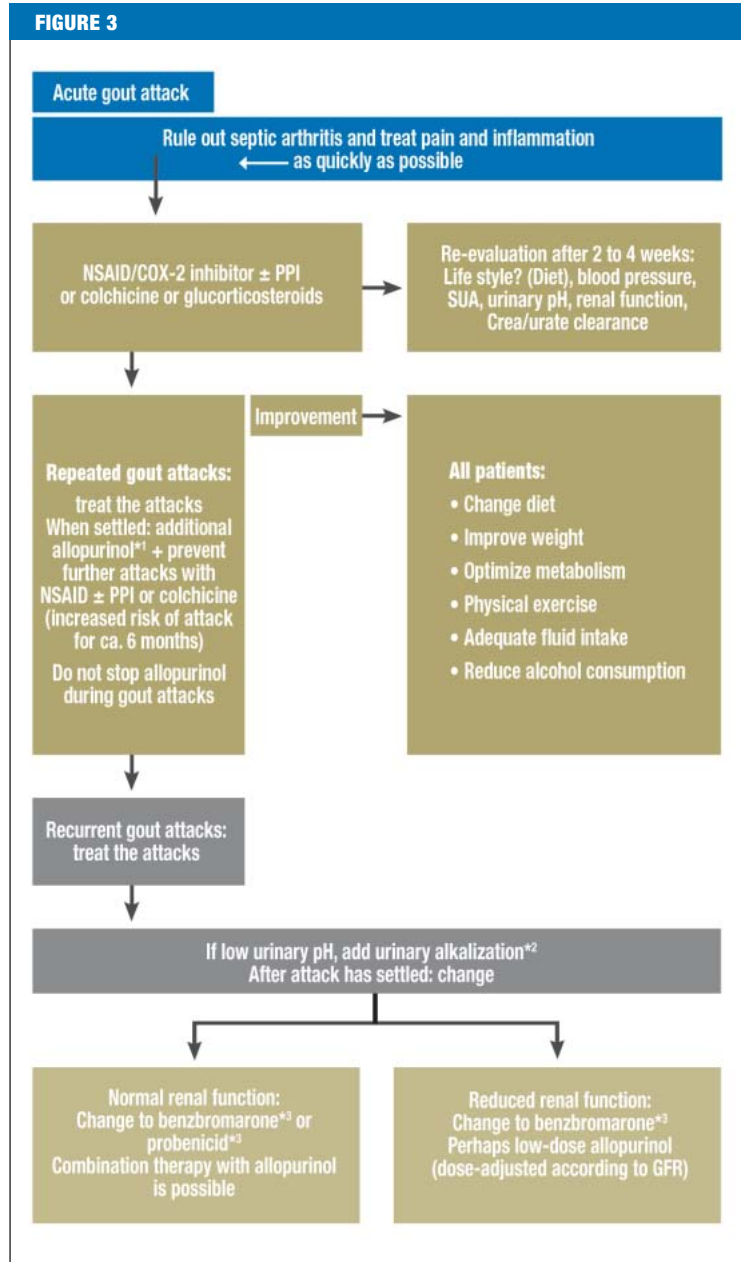
Treatment algorithm for gout
*1 Dose titration of allopurinol depending on serum urate level, up to a maximum of 800 mg/d with monitoring of renal function; *2 urinary alkalization using citrate compounds to prevent urate stones (EL III); *3 not available in Austria and Switzerland; COX-2, cyclooxygenase-2; PPI, proton pump inhibitor; SUA, serum urate; Crea, creatinine; GFR, glomerular filtration rate; modified from (19)

As a rule, urate reduction needs to be continued for several years, often life-long; however, this is a decision that needs to be made individually in each case (e18, e38, e39). Controlled urate-lowering therapy carried out over a long period results in patients remaining free of attacks for a long time after treatment has ceased (EL III) (25, e40). It is important to monitor serum urate concentrations regularly during the treatment (EL IV) (7, 19).

TABLE 4

Treatment for acute gout attack. Evidence levels (EL) are shown in parentheses

Therapeutic option (evidence level)	Comments/concerns	Complications of long-term continuation of treatment
Nonpharmacological (EL III)	Rest, raise the limb, topical application of ice	
NSAID/COX-2 inhibitor (± PPI) (EL Ib)	Not for patients with gastrointestinal ulcer or bleeding, NSAID-induced asthma or impaired renal function Interaction with coumarin/warfarin	Gastrointestinal side effects, renal effects
Colchicine (EL Ib)	Care is needed in patients with hepatobiliary dysfunction, acute infections, or age over 70 years Drug interactions Watch out for: diarrhea, gastrointestinal intolerance, and local tissue necrosis	Potential for serious side effects
Glucocorticosteroids (EL Ib)	Deterioration of diabetic metabolism in patients with diabetes mellitus Possible need for additional anti-inflammatory substances/analgesia or use of moderate to high doses	High blood pressure Raised blood sugar Osteoporosis Gastrointestinal side effects

Future prospects

The recently licensed xanthine oxidase inhibitor febuxostat appears to be an alternative treatment for example in patients with allopurinol intolerance, contraindications for uricosurics, or when uricosurics are unavailable (benzbromarone and probenecid are not available in Austria and Switzerland). An advantage is that febuxostat can be used in patients with renal failure as it is metabolized in the liver. Current studies have shown that with a comparable side-effects profile, more effective urate reduction is achieved: 53% of patients given febuxostat 80 mg/d and 62% of those given 120 mg/d had serum urate concentrations below 360 µmol/L (6.0 mg/dL), compared to 21% of those treated with 300 mg/d allopurinol. However, it could not be shown that febuxostat was superior to allopurinol in reducing gout attacks as a clinical parameter (e41, e42). Febuxostat would therefore be a candidate alternative drug for use when allopurinol cannot be used because of intolerance or other contraindications, or when uricosuric treatment has reached its limits or is not possible. As a novel drug, the daily treatment costs will no doubt be much higher than those of allopurinol (which are a matter of cents).

Therapy using recombinant uratoxidase or its longer-acting pegylated form to degrade urate into the easily water-soluble allantoin is at present licensed only for use in tumor lysis syndrome. Partly because of large numbers of severe anaphylactic reactions due to possible antigenicity caused by an animal element, and because of high costs amounting to around 10 000 euros/year, this treatment can only be considered off-label in rare cases of severe tophaceous gout. First results of phase 2 studies have been published (e43, e44).

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