REVIEW ARTICLE

Treatment Options for Gout

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SUMMARY

Background: 1–2% of adults in Germany suffer from gout. Gout is one of the few rheumatological diseases that can be cured. It arises through the deposition of uric acid crystals in joints as a result of hyperuricemia. Painful redness and swelling of the affected joints are typical findings. Multiple pertinent guidelines and treatment recommendations have been published, but there is reason to believe that patients with gout are not always treated accordingly.

Methods: This review is based on relevant publications from the years 2000–2016 that were retrieved by a selective search in the Cochrane and PubMed databases.

Results: In a person with normal renal function, asymptomatic hyperuricemia is not an indication for treatment to lower the serum uric acid level. The drugs of first choice for acute gouty arthritis are nonsteroidal anti-inflammatory drugs (NSAID), corticosteroids, and colchicine. Treatment with xanthine oxidase inhibitors (XOI) or uricosuric drugs is indicated for patients with a recurrent or severe course; the target uric acid value is <6 mg/dL. Long-term treatment should be initiated only after resolution of the acute attack. For patients with refractory gout, lesinurad (approved in February 2016) in combination with XOI is a new treatment option that can be considered. Comprehensive patient education and counseling is an important component of the treatment of patients with gout. Regular laboratory follow-up is necessary as well.

Conclusion: The prevalence of gout is rising around the world. Patients with gout could benefit greatly from consistent implementation of the existing treatment guidelines and recommendations. In the future, controlled trials should be conducted to determine the best time to start treatment and the optimal target level for the serum uric acid concentration in terms of a risk/benefit analysis.

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Approximately 1 to 2% of adults in Germany suffer from gout and around 20% from hyperuricemia. This makes gout the most widespread form of arthritis nationwide (1). It is one of the few rheumatic diseases that can be cured. Gout is caused by the deposition of uric acid crystals in joints or in tissues around joints as a result of hyperuricemia. Typically, painful swelling and reddening occur in the affected joint. An increase in the prevalence and incidence of gout has been observed worldwide (e1). There is no data on Germany specifically. However, because current incidence levels are similar to the incidence found in Annemans' study (1), it can be inferred that the situation in Germany is the same. Attention has shifted back to gout for both health-related and economic reasons (1, 2, e1). In the past, multiple guidelines and treatment recommendations were published in order to improve care for gout patients. However, care currently fails to comply with these guidelines in a number of ways. These include overuse of allopurinol for asymptomatic patients with hyperuricemia and a failure to monitor uric acid-lowering drug therapy. Multiple studies have shown this discrepancy between treatment recommendations and clinical practice (3, 4, e1–e3).

Methods

The authors performed a selective search of the literature for the years 2000 to 2016 in the Cochrane Database and in PubMed. In PubMed the following search terms were used: "gout" OR "hyperuricemia"; filters activated: "meta-analysis," "systematic reviews," "randomized controlled trial," "guideline," "clinical trial," "abstract," "publication date from 2000/01/01," "humans," "English," "German." The initial search yielded 628 hits. Following the analysis of titles and abstracts, 159 sources remained; these were used as the basis for a qualitative synthesis. Some older, basic publications were added individually. A detailed description of the procedure, which complied with the PRISMA (preferred reporting items for systematic reviews and meta-analyses) Statement, is available from the authors.

Results

Our search yielded little literature of high quality in terms of level of evidence and study design. This article states the grade of each recommendation according to the most recent guidelines (5, 6) in parentheses.

Definitions

Gout is divided into 4 stages (e4):

- Asymptomatic deposits in tissues

TABLE 1

Gout incidence by serum uric acid level*

Serum uric acid (mg/dL)	Incidence (%/year)
<7	0.1
7.0 to 8.9	0.5
≥ 9	4.9

*according to Campion et al. (9)

- Acute gout: This is defined as rapidly-developing inflammation, usually of only one joint, with painful overheating and swelling. Uric acid crystals trigger the inflammation reaction in joints or tissues around joints.
- Intercritical periods: These are clinically inactive disease phases between 2 flares. During these periods, gout patients also have hyperuricemia, which can lead to increased deposition of urate crystals in tissues. Intercritical periods become shorter as the disease progresses.
- Chronic gout: This is characterized by long-term joint inflammation, which leads to joint pain at rest and/or on movement.

Prevalence

According to the European League Against Rheumatism (EULAR), the prevalence of symptomatic gout among the adult Western population is 1 to 2% (7), rising to 7% in those aged over 65 years (1). Publications to date do not give prevalence figures for individual stages of gout.

Etiology

Gout can be caused by overproduction of uric acid (10% of cases) or lowered renal uric acid excretion (90%) (e5). Rarer causes of gout are genetic purine metabolism disorders such as the Lesch–Nyhan syndrome (e6).

Uric acid is the end product of purine metabolism in humans. The solubility product of uric acid at 37 °C is 6.8 mg/dL (8). Hyperuricemia can favor the precipitation

TABLE 2

Diagnosis criteria for gout*

Criterion	Characteristics	Points
Pattern of involvement	Ankle/foot MTP-1	1 2
Symptoms: – Erythema of joint – Affected joint very sensitive to touch – Movement very limited	 1/3 symptoms 2/3 symptoms All 3 symptoms	 1 2 3
Criteria for typical episode: – Pain develops within 24 hours – Resolves after ≤14 days – Complaint-free intervals	 1 typical episode Multiple typical episodes	 1 2
Evidence of tophus	Present	4
Laboratory tests: – Serum uric acid (preferably without treatment, 4 weeks before/after an episode or highest value during episode) – Joint fluid analysis following puncture (if performed)	 <4 mg/dL 6 to 8 mg/dL >8 to <10 mg/dL ≥10 mg/dL No urate crystals	 –4 2 3 4 –2
Imaging: – Urate deposits on ultrasound or DECT – Erosions characteristic of gout on conventional X-ray	 Present Present	 4 4

According to Neogi et al. (12)
*If swelling score is 8 or more out of a maximum of 23 points, arthritis can be classified as gout with a sensitivity of 92% and a specificity of 89%. Evidence of uric acid crystals on puncture is a sufficient criterion.
DECT: Dual-energy computed tomography; MTP-1: Metatarsophalangeal joint I

of urate crystals in tissues, leading to gout. Incidence of gout rises with uric acid level (9) *(Table 1)*. Uric acid crystals precipitate faster at lower temperatures, so toes, fingers, hands, feet, elbows, and ears are the principal sites of gout flares and deposition of uric acid crystals in soft tissues (gout tophi). Uric acid crystals may also be deposited in the urinary tract (urolithiasis).

The uric acid crystals that have precipitated lead to inflammasome activation in monocytes and the subsequent release of various inflammatory mediators such as interleukin-1 (10). If left untreated, an acute gout flare lasts between 3 days and 2 weeks. A patient's first gout flare is monoarthritis in up to 90% of cases, most commonly inflammation of the joint at the base of the big toe (podagra) (11). Polyarthritis is more common in older patients (4).

Diagnosis

In primary care practice, a gout flare is diagnosed on the basis of examination (typical pattern of involvement) and medial history (after ruling out red flags: trauma, condition following intra-articular injection, surgery, fever, poor general health) (e7). In 2015 the US and European rheumatology societies (the American College of Rheumatology [ACR] and EULAR respectively) developed a clinical diagnosis score (12) *(Table 2)*. These diagnosis criteria state that evidence of uric acid crystals on joint puncture is sufficient to confirm a diagnosis of gout. Due to risk/benefit considerations, these authors advise against diagnostic puncture where clinical findings unambiguously indicate a gout flare (C).

Laboratory and X-ray analysis

One-third of patients with an acute gout flare have normal uric acid levels (e8). A normal serum uric acid level in cases of acute arthritis does not rule out gouty arthritis. A high uric acid level increases the probability of gouty arthritis but does not confirm the diagnosis (12) (C). In an acute gout flare, uric acid precipitates and, as uric acid crystals, causes the patient's complaints; this may lead to a reduction in the measurable blood uric acid level. Uric acid level measurement a few weeks after a flare in order to monitor disease progression is recommended (13) (B).

Laboratory tests may be necessary for further clarification in cases of atypical progression or for differential diagnosis. The following diseases must be considered in differential diagnosis of acute gout:

- Septic arthritis
- Trauma
- Active arthritis
- Pseudogout
- Rheumatoid arthritis

Annual laboratory tests, particularly of retention levels and uric acid level, should be performed to monitor the progression of chronic gout (14) (B).

To date, conventional imaging has not played a major role in primary diagnosis, as gout does not cause

BOX

Dietary recommendations for gout (16, e13)

- Overweight patients should aim for a normal weight but should not crash-diet or follow protein-rich diets such as the Atkins diet.
- Reduced-fat foods and vegetarian sources of protein should be integrated into the diet.
- Protein-rich foods such as meat, offal, crustaceans, and yeast should be avoided.
- Patients known to suffer from gout and kidney stones should be instructed to consume sufficient fluids (>2 L /day).
- Consumption of alcohol, particularly beer and spirits, should be reduced. Patients should be encouraged to refrain from consuming alcohol on at least 3 days per week.
- Sugar-sweetened beverages should be avoided. One study showed that consumption of soft drinks and drinks containing fructose entailed an increased risk of a gout flare (e14). Fructose inhibits uric acid excretion by the kidneys.

TABLE 3

Treatment options for acute gout

Substance/group	Proposed therapy	Adverse drug effects	Major contraindications	Recommendation grade	Comments
Nonsteroidal anti-inflammatory drugs (NSAIDs) PO	Maximum dose; 5 to 10 days or until symptoms resolve	Renal dysfunction	Renal failure	(A) Cochrane review: NSAID treatment option for acute gout flare (19)	Early start of treatment more important than choice of NSAID
Corticosteroids PO	30 to 35 mg prednisolone PO for 5 days	Overproduction of stomach acid, Cushing's syndrome, metabolism disorder, hypertension/hypotension	– Infection in particular – Poorly managed diabetes mellitus or arterial hypertension – Ulcerating wound(s)	(A) RCT: Corticosteroids have no disadvantages versus NSAIDs (20)	
Colchicine PO	Low-dose therapy: 2 × 0.5 mg initially, then single administration 0.5 mg after 1 hour	Gastrointestinal effects in particular	Reduced creatinine clearance or liver failure; concomitant administration of CYP3A4 inhibitors, e.g. statins (5, 21)	(A) RCT: Low-dose therapy has the same clinical effect as higher dose and fewer adverse effects (22)	If gout flare was no longer than 24 hours ago
Cortisone IA or IM		Overproduction of stomach acid, Cushing's syndrome, metabolism disorder, hypertension/hypotension		(B) Cochrane review: no evidence to date of clinically significant superiority over oral corticosteroid therapy (23)	IM or IA corticosteroid injection possible in exceptional cases
Interleukin-1 antagonists Canakinumab SC	Single administration (150 mg SC), repeat administration after no less than 12 weeks (24)	Infections (e.g. urinary tract infections, airway infections); local skin reactions at site of injection	If active infections present	(B) Cochrane review: more effective than 40 mg triamcinolone IM (24)	If all 3 standard treatment options contraindicated/not tolerated

IA: Intra-articular; IM: Intramuscular; NSAID: Nonsteroidal anti-inflammatory drug; PO: Per os; SC: subcutaneous; RCT: Randomized controlled trial

radiologically visible bone changes until it has progressed to a late stage (e9). Earlier detection of tophi in soft tissues may be used to monitor treatment in the future. Ultrasound examination can be used as a noninvasive option. Sonography shows synovialitis with markedly increased vascularization and a double contour sign. (e10, 15). Dual-energy CT (DECT) can reveal small deposits of uric acid crystals but should only be considered if findings for differential diagnoses are unclear, as it involves radiation exposure, is expensive, and has low overall sensitivity (15) (C).

Treatment

Gout treatment rests on 2 pillars: nonpharmacological and pharmacological therapy. How much of each should be used depends on the individual patient's needs. Stage (acute gout, intercritical phase, or chronic gout), individual factors (number of flares, radiological findings), and general risk factors play a crucial role in this.

Nonpharmacological therapy

This includes patient education, dietary recommendations, and resting the joint.

Patient education (C): One approach to gout treatment is patient education. Hyperuricemia is more common with current lifestyle trends (increasing lack of exercise, excess weight). A cohort study conducted in England showed that detailed education led to successful gout management by patients (e11).

Dietary recommendations: Diet affects uric acid levels. Changes to diet and lifestyle can reduce uric acid levels by up to 18% (16). Several studies have shown that less than 50% of gout patients surveyed were informed of the association between particular foods and gout (e12).

Many authors recommend the same diet as for cardiovascular event prevention (www.degam.de/patienten informationen.html—in German). A large cohort study has shown that weight loss and subsequently improved metabolic status can also reduce the incidence of gout flares (e13) (B). Dietary recommendations *(Box)* are based on pathophysiological considerations and are compatible with other healthy dietary recommendations. No randomized controlled trials have yet investigated whether the recommendations have a positive effect on patients' gout progression (17).

Resting the joint: A systematic review showed that correct rest for the joint can also contribute to the treatment of an acute gout flare. The affected joint should be raised and cooled (18) (C).

Pharmacological therapy for acute gout

Pharmacological therapy for acute gout aims to achieve an absence of pain and resolution of joint inflammation as rapidly as possible. Without pharmacological treatment, a gout flare lasts between 3 days and 2 weeks. In general, anti-inflammatory therapy should be begun immediately, preferably within 12 to 24 hours of onset of an acute gout flare (B). First-line treatment options are nonsteroidal anti-inflammatory drugs (NSAIDs),

TABLE 4

Treatment options for chronic gout

Substance/group	Proposed therapy	Adverse drug effects	Major contraindications	Recommendation grade	Comments
Xanthine oxidase inhibitor: allopurinol	Initially 50 to 100 mg/day; increase to max. 800 mg/day	Diarrhea, nausea, vomiting, increased liver enzymes, skin reactions (2%), hypersensitivity syndrome (0.1%) (e17)	Known hypersensitivity to allopurinol	(A) Cochrane review: target serum uric acid levels achieved more frequently with allopurinol than with placebo (33)	Adjust dose in cases of known renal failure *(eTable)* Monitor liver and kidney enzyme levels
Xanthine oxidase inhibitor: febuxostat	Initially 80 mg/day, increase to 120 mg/day if necessary	Liver dysfunction, diarrhea, nausea, headache, skin rash	Ischemic heart disease <12 months or decompensated heart failure (32, 34, e19)	(A) Cochrane review: lowers uric acid levels more effectively than allopurinol (34)	If allopurinol not tolerated, in cases of renal failure, or if target uric acid level not achieved despite increased allopurinol dose (A)
Uricosuric agent: probenecid	Probenecid can be combined with allopurinol if allopurinol alone is insufficiently effective (5)	Irritation of gastrointestinal tract, skin reactions, anorexia	Urolithiasis, advanced renal failure (creatinine clearance <50 mL/min), or increased uric acid production (e.g. during chemotherapy) (5, 14)	(B) There are no placebo-controlled trials of uricosuric agents. RCT (35): probenecid less effective than allopurinol	Take with sufficient fluids to prevent kidney stone formation
Selective inhibitor of URAT1 transporter: lesinurad	Authorized in combination with xanthine oxidase inhibitor for treatment-refractory cases since February 2016 (36)	Headache, influenza-like symptoms increased creatinine levels, gastroesophageal reflux	Severe renal failure, tumor lysis syndrome, Lesch–Nyhan syndrome	(B) RCT: lowers uric acid levels more effectively in combination with allopurinol (37)	Further studies required on cardiovascular safety according to the European Medicines Agency (EMA) (e20). Therefore not currently recommended by these authors for patients with cardiovascular events <12 months (C).
Uricosuric agent: benzbromarone		Not recommended by these authors due to liver toxicity (38) (C)			
Uricase: pegloticase	Taken off the market in July 2016 (e21)	Uric acid levels reduced due to breakdown of uric acid into allantoin, which is eliminated in the urine. Adverse drug effects: infusion issues, anaphylaxis, antibody formation.			

RCT: Randomized controlled trial

glucocorticoids, and colchicine (5) (A). Treatment usually relieves symptoms after 24 hours (19). The decision which of the 3 substance groups to use depends on the patient's comorbidities and the physician's experience. *Table 3* provides an overview of treatment options.

In addition, it is recommended that treatment with drugs that induce hyperuricemia, particularly diuretics and low-dose acetylsalicylic acid, should not be begun in patients with acute gout, and that the dose of established therapy should not be increased (5, 16) (B).

Gout patients occasionally suffer from comorbidities that are incompatible with NSAID, colchicine, or cortisone treatment. Recent studies have shown that interleukin-1 is an important mediator of inflammation in acute gout. According to a Cochrane review (24), interleukin-1 antagonists can be considered as an alternative option if all 3 standard treatment options are contraindicated or not tolerated (B).

Uric acid-lowering drugs used to treat chronic gout are contraindicated for the treatment of acute gout flares, as they can also cause acute gout flares (25) (C). Long-established uric acid-lowering therapy should continue to be administered during an acute gout flare.

Treatment of asymptomatic hyperuricemia

Studies published to date indicate that treatment for asymptomatic hyperuricemia in patients with healthy kidneys cannot be recommended (26) (C). Two meta-analyses indicate an increase in cardiovascular risk in particular for hyperuricemia patients (e15, 21). However, there are no available studies that yield an unambiguous conclusion. In *in vitro* studies, uric acid has shown an antioxidant and therefore protective effect (e16). Further studies on this are required.

Chronic gout treatment

Chronic gout treatment should aim to prevent gout progression and further gout flares, to eliminate any urate deposits, and to reverse tophus formation. International guidelines recommend that uric acid levels be adjusted to well below the solubility limit of 6.8 mg/dL in order

to prevent deposits (14, 16, e11). There are currently no available studies that have investigated the optimum target uric acid levels. The German College of General Practitioners and Family Physicians (DEGAM, *Deutsche Gesellschaft für Allgemeinmedizin*) recommends that uric acid levels should be maintained below 6.5 mg (27). The EULAR advises uric acid levels of less than 6 mg/dL, and even as low as <5 mg/dL in patients with severe gout (B). Lifelong therapy is recommended. A prospective cohort study has shown that withdrawal can be attempted after uric acid levels have successfully been maintained at a low level for more than 5 years (28) (B).

Long-term therapy should begin no sooner than 2 weeks after the beginning of an acute gout flare (B).

Long-term therapy is recommended for patients with the following symptoms (16, 27) (B):

- More than 2 gout flares per year
- Urolithiasis and gout
- Known overproduction of uric acid, e.g. during chemotherapy
- Pre-existing tophi

According to EULAR recommendations, the option of beginning treatment early should be discussed with patients in order to reduce crystallization if gout does continue to progress (6). However, there is no clear evidence supporting this. Because allopurinol also has side effects and can lead to increased gout flares, particularly after the beginning of treatment, these authors recommend that patients should first try to reduce their uric acid levels through lifestyle changes.

Increased gout flares may occur in the first weeks to months after the beginning of uric acid-lowering treatment. When serum uric acid levels fall, uric acid deposits are mobilized from the tissues (e8, 29, 30). There are no randomized controlled trials on gout flare prophylaxis. Current knowledge has been obtained from febuxostat authorization studies and other sources (5). More gout flares have been described after the beginning of febuxostat treatment than of allopurinol treatment; however, there are no significant differences after longer-term administration. It is recommended that uric acid-lowering treatment be begun with a gradual dose increase (6) (C). Low-dose colchicine (0.5 mg/day) or a low-dose NSAID is recommended for 6 months to prevent flares (31, 32) (B).

International guidelines describe xanthine oxidase inhibitors as first-line treatment and uricosuric agents as second-line treatment. The leading xanthine oxidase inhibitor and uricosuric agent are allopurinol and probenecid respectively. Possible treatment options are listed in *Table 4*. A higher proportion of patients achieve the target uric acid level of 6 mg/dL with febuxostat—which is also a xanthine oxidase inhibitor—than with allopurinol (48% versus 22% [32]). Febuxostat is therefore a possible option for treatment-refractory hyperuricemia. Should this escalation be insufficient, combination therapy with a xanthine oxidase inhibitor and lesinurad, a selective inhibitor of the URAT1 transporter, is possible. In general, regular laboratory testing should be performed to monitor treatment success, and treatment should be adjusted if necessary (C). Urate oxidase should also be mentioned as a treatment option for treatment-refractory patients. However, this drug was taken off the market in mid-2016.

Discussion

Despite the high prevalence of gout, there have been only a few randomized clinical trials on which conclusions can be based to aid the development of evidence-based medicine. Recommendations are often based on pathophysiological considerations. There is a clear need to fill in the gaps.

Some questions have not yet been researched conclusively, such as the effect of uric acid on the human body. For clinical practice it is of interest whether asymptomatic hyperuricemia is an independent cardiovascular risk factor or whether very low uric acid levels over long periods have an adverse effect on the central nervous system. Further research is also needed on the effect of uric acid on renal function. In summary, controlled trials on optimum uric acid level should be conducted, involving risk/benefit analysis of serum uric acid.

Further studies from which conclusions can be drawn researching the optimum time to begin treatment for chronic gout would also be of practical interest. Can uric acid-lowering therapy be started as early as during an acute gout flare? To date, only one, single-center study with a total of 57 patients has addressed this question (e22). This found no adverse effect on the frequency of gout flares as a result of beginning uric acid-lowering therapy early (less than 7 days after the beginning of a gout flare).

After a long hiatus in treatment options, there are now new options on the market. How useful they are remains to be seen.

A new drug for the treatment of acute gout is the IL-1 antagonist canakinumab. This is authorized for use when the 3 standard treatment options (NSAIDs, corticosteroids, and colchicine) are not tolerated, insufficiently effective, or contraindicated. Newly on the market for chronic gout is lesinurad, which is authorized for use in combination with a xanthine oxidase inhibitor for patients whose gout is refractory to standard treatment (a xanthine oxidase inhibitor or probenecid).

Conclusion for clinical practice

It is important to respond to gout appropriately at an early stage in order to avoid painful, chronic disease for patients. To improve compliance, particular emphasis should be placed on educating and involving patients. Regular laboratory testing should be performed during treatment to monitor progression. Withdrawal may be attempted after therapy has successfully lowered uric acid levels for several years.

KEY MESSAGES

- Increased uric acid levels that are not causing a disease such as gout or urolithiasis are not an indication for pharmacotherapy (C).
- Acute gout requires pharmacotherapy (nonsteroidal anti-inflammatory drugs, corticosteroids, or colchicine). Optimum results are achieved if pharmacotherapy is begun as soon as possible, preferably within 12 to 24 hours of onset of pain (B).
- After a first gout flare the patient should be informed of possible lifestyle changes. Patient education should be provided to improve compliance (C).
- Nonpharmacological treatment (raising and cooling the joint) can be recommended concomitantly (C).
- The literature recommends beginning long-term treatment no sooner than 2 weeks after an acute gout flare if the following symptoms are present (B):
  - More than 2 gout flares per year
  - Urolithiasis and gout
  - Known overproduction of uric acid, e.g. during chemotherapy
  - Tophi

Conflict of interest statement
The authors declare that no conflict of interest exists.

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REFERENCES

1. Annemans L, Spaepen E, Gaskin M, et al.: Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000–2005. Ann Rheum Dis 2007; 67: 960–6.
2. Kuo C, Grainge MJ, Zhang W, Doherty M: Global epidemiology of gout: prevalence, incidence and risk factors. Nat Rev Rheumatol 2015; 11: 649–62.
3. Cottrell E, Crabtree V, Edwards JJ, Roddy E: Improvement in the management of gout is vital and overdue: an audit from a UK primary care medical practice. BMC Fam Pract 2013; 14: 170.
4. Engel B, Bleckwenn M, Weckbecker K: [How do family practitioners treat gout? Results of a survey in NRW]. Z Allg Med 2014; 90: 277–81.
5. Kiltz U, Alten R, Fleck M, et al.: Langfassung zur S2e-Leitlinie Gichtarthritis (fachärztlich). Rheumatol 2016; 75: 11.
6. Richette P, Doherty M, Pascual E, et al.: 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2017; 76 : 29–42
7. Zhang W, Doherty M, Bardin T, et al.: EULAR evidence based recommendations for gout. Part I: Diagnosis. Report of a task force of the standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006; 65: 1301–11.
8. Terkeltaub RA: Gout. N Engl J Med 2003; 349: 1647–55.
9. Campion E, Delabry L: Asymptomatic hyperuricemia. Risks and consequences in the normative aging study. Am J Med 1987; 82: 421–6.
10. Krishnan E: Inflammation, oxidative stress and lipids: the risk triad for atherosclerosis in gout. Rheumatology (Oxford) 2010; 49: 1229–38.
11. Taylor W, Fransen J, Jansen T, et al.: Study for updated gout classification criteria (SUGAR): identification of features to classify gout. Arthritis Care Res (Hoboken) 2015; 67: 1304–15.
12. Neogi T, Jansen T, Dalbeth N, et al.: 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis Rheumatol 2015; 67: 2557–68.
13. Tausche A, Jansen TL, Schröder HE, Bornstein SR, Aringer M, Müller-Ladner U: Gout—current diagnosis and treatment. Dtsch Arztebl Int 2009; 106: 549–55.
14. Zhang W, Doherty M, Pascual E, et al.: EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis 2006; 65: 1312–24.
15. Parathithasan N, Lee W, Pianta M, Oon S, Perera W: Gouty arthropathy: review of clinicopathologic and imaging features. J Med Imaging Radiat Oncol 2016; 60: 9–20.
16. Khanna D, Fitzgerald JD, Khanna PP, 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.
17. Moi JHY, Sriranganathan MK, Edwards CJ, Buchbinder R: Lifestyle interventions for chronic gout. Cochrane Database Syst Rev 2013; 5: CD010039.
18. Moi JHY, Sriranganathan MK, Edwards CJ, Buchbinder R: Lifestyle interventions for acute gout. Cochrane Database Syst Rev 2013; 11: CD010519.
19. van Durme CMPG, Wechalekar MD, Buchbinder R, Schlesinger N, van der Heijde D, Landewé RBM: Non-steroidal anti-inflammatory drugs for acute gout. Cochrane Database Syst Rev 2014; 9: CD010120.
20. Janssens HJEM, Janssen M, van de Lisdonk EH, van Riel PLCM, van Weel C: Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. Lancet 2008; 371: 1854–60.
21. Stack A, Hanley A, Casserly L: Independent and conjoint associations of gout and hyperuricaemia with total and cardiovascular mortality. Q J Med 2013; 106: 647–58.
22. Terkeltaub RA: High versus low dosing of oral colchicine for early acute gout flare: twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. Arthritis Rheum 2010; 62: 1060–8.
23. Wechalekar MD, Vinik O, Schlesinger N, Buchbinder R: Intra-articular glucocorticoids for acute gout. Cochrane Database Syst Rev 2013; 4: CD009920.
24. Sivera F, Wechalekar MD, Andrés M, Buchbinder R, Carmona L: Interleukin-1 inhibitors for acute gout. Cochrane Database Syst Rev 2014; 9: CD009993.
25. Khanna D, Khanna PP, Fitzgerald JD, 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 (Hoboken) 2012; 64: 1447–61.
26. Vinik O, Wechalekar M, Falzon L, Buchbinder R, van der Heijde D, Bombardier C: Treatment of asymptomatic hyperuricemia for the prevention of gouty arthritis, renal disease, and cardiovascular events: a Systematic literature review. J Rheumatol 2014; 92: 70–4.
27. Engel B, Prautzsch H: [Management of gout—new guidelines published by the German College of General Practitioners and Family Physicians (DEGAM)]. Z Allg Med 2014; 90: 7–12.
28. Perez-Ruiz F, Atxotegi J, Hernando I, Calabozo M, Nolla J: Using serum urate levels to determine the period free of gouty symptoms after withdrawal of long-term urate-lowering therapy: a prospective study. Arthritis Rheum 2006; 55: 786–90.

29. Becker MA, Schumacher HR, Wortmann RL, et al.: Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005; 353: 2450–61.
30. Borstad GC, Bryant LR, Abel MP, et al.: Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. J Rheumatol 2004; 31: 2429–32.
31. Wortmann R, MacDonald P, Hunt B, Jackson R: Effect of prophylaxis on gout flares after the initiation of urate-lowering therapy: analysis of data from three phase III trials. Clin Ther 2010; 32: 2386–97.
32. Schumacher R, Becker M, Wortmann R, 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: 1540–8.
33. Seth R, Kydd ASR, Buchbinder R, Bombardier C, Edwards CJ: Allopurinol for chronic gout. Cochrane Database Syst Rev 2014; 10: CD006077.
34. Tayar JH, Lopez-Olivo MA, Suarez-Almazor ME: Febuxostat for treating chronic gout. Cochrane Database Syst Rev 2012; 11: CD008653.
35. Reinders M, Haagsma C, Jansen T: A randomised controlled trial on the efficacy and tolerability with dose escalation of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout. Ann Rheum Dis 2009; 68: 892–7.
36. Fleischmann R, Kerr B, Yeh L, et al.: Pharmacodynamic, pharmacokinetic and tolerability evaluation of concomitant administration of lesinurad and febuxostat in gout patients with hyperuricemia. Rheumatology (Oxford) 2014; 53: 2167–74.
37. Saag KG, Fitz-Patrick D, Kopicko J, et al.: Lesinurad combined with allopurinol: randomized, double-blind, placebo-controlled study in gout subjects with inadequate response to standard of care allopurinol (a US-based study). Arthritis Rheumatol 2017; 69: 203–12.
38. Kaufmann P, Török M, Hänni A, Roberts P, Gasser R, Krähenbühl S: Mechanisms of benzarone and benzbromarone-induced hepatic toxicity. Hepatology 2005; 41: 925–35.

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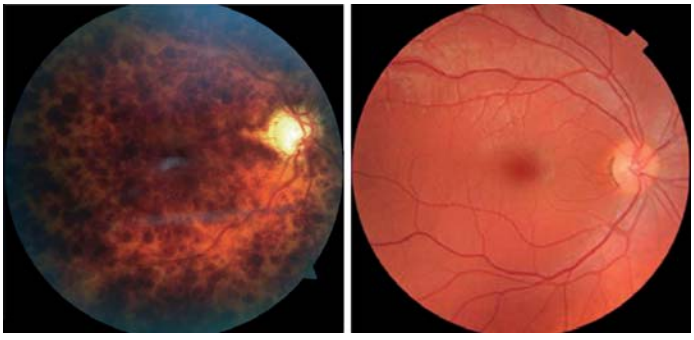
CLINICAL SNAPSHOT

Sudden Unilateral Impairment of Vision



Fundoscopic image: the optic papilla is yellowish-white, intraretinal hemorrhages are seen all over the retina (dark spots), and the veins are engorged. Normal findings at right.

A 77-year-old woman presented to a hospital ophthalmology service with sudden impairment of vision in the right eye. In a test of visual acuity, she could only read the upper lines of the eye chart with the right eye. Fundoscopy revealed disseminated intraretinal hemorrhages and macular edema due to central retinal vein occlusion. She underwent eye surgery for the intravitreal administration of a VEGF inhibitor, as well as isovolemic hemodilution. An assessment for cardiovascular risk factors was positive for smoking (60 py), hypercholesterolemia (296 mg/dL), and WHO stage I arterial hypertension; none of these conditions had been treated.

Central retinal vein occlusion usually arises in persons with advanced vascular disease. The affected patients should undergo cardiovascular evaluation.

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Conflict of interest statement
The authors declare that no conflict of interest exists.

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Supplementary material
For eReferences please refer to:
www.aerzteblatt-internatioanl.de/ref1317

eTable:
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Treatment Options for Gout

by Bettina Engel, Johannes Just, Markus Bleckwenn, and Klaus Weckbecker

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eReferences

e1. Roddy E, Zhang W, Doherty M: The changing epidemiology of gout. Nat Clin Pract Rheumatol 2007; 3: 443–9.

e2. Wise E, Khanna PP: The impact of gout guidelines. Curr Opin Rheumatol 2015; 27: 225–30.

e3. Singh JA, Hodges JS, Asch SM: Opportunities for improving medication use and monitoring in gout. Ann Rheum Dis 2009; 68: 1265–70.

e4. National Center for Chronic Disease Prevention and Health Promotion, Division of Population Health: Gout. www.cdc.gov/arthritis/basics/gout.htm (last accessed on 25 September 2016).

e5. Choi HK: A prescription for lifestyle change in patients with hyperuricemia and gout. Curr Opin Rheumatol 2010; 22: 165–72.

e6. Dincer HE, Dincer AP, Levinson DJ: Asymptomatic hyperuricemia: to treat or not to treat. Clev Clin J Med 2002; 69: 594.

e7. Janssens H, Fransen J, van de Lisdonk E, van Riel P, van Weel C, Janssen M: A diagnostic rule for acute gouty arthritis in primary care without joint fluid analysis. Arch Intern Med 2010; 170: 1120–6.

e8. Jordan RW, Khan SA: The management of gout in primary care. InnovAiT 2012; 5: 503–8.

e9. Reuss-Borst M: [Differential diagnosis and therapy of gout]. Med Klin (Munich) 2009; 104: 710–20.

e10. Dalbeth N, Doyle AJ: Imaging of gout—an overview. Best Pract Res Clin Rheumatol 2012; 26: 823–38.

e11. 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.

e12. Roddy E, Zhang W, Doherty M: Concordance of the management of chronic gout in a UK primarycare population with the EULAR gout recommendations. Ann Rheum Dis 2007; 66: 1311–5.

e13. Choi H, Atkinson K, Karlson E, Curhan G: Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med 2005; 165: 742–8.

e14. Choi H, Curhan G: Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. BMJ 2008; 336: 309–12.

e15. Goicoechea M, de Vinuesa S, Verdalles U: Effect of allopurinol in chronic kidney disease progression and cardiovascular risk. Clin J Am Soc Nephrol 2010; 5: 1388–93.

e16. Ames B, Cathart R, Schwiers E, Hochstein P: Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: a hypothesis. Proc Natl Acad Sci USA 1981; 78: 6858–62.

e17. Stamp L, Day R, Yun J: Allopurinol hypersensitivity: investigating the cause and minimizing the risk. Nat Rev Rheumatol 2016; 12: 235–42.

e18. Pazár Maldonado B, So A: Ätiologie und Management der Gicht. Z Rheumatol 2012; 71: 127–37.

e19. Frampton J: Febuxostat: a review of its use in the treatment of hyperuricaemia in patients with gout. Drugs 2015; 75: 427–38.

e20. EMA Risk Management Plan Lesinurad. www.ema.europa.eu/ema/index.jsp?curl=search.jsp&q=EMA%2F1488%2F2016&btnG=Search&mid= (last accessed on 25 September 2016).

e21. EMA public statement, 21 July 2016 EMA/498114/2016. www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2016/07/WC500210911.pdf (last accessed on 25 September 2016).

e22. Taylor T, Mecchella J, Larson R, et al.: Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. Am J Med 2012; 125: 1126–1134.e7.

eTABLE

Dosing of allopurinol for patients with kidney failure

Creatinine clearance (mL/min)	Daily allopurinol dose (mg)
100	300
80	250
60	200
40	150
20	100
10	100 every other day
0	100 every 3 days
Hemodialysis (2 to 3 times/week)	300 soon after each dialysis session

According to Pazár Maldonado and So (e18)