CLINICAL PRACTICE

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Gout

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This Journal *feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author s clinical recommendations.*

A 64-year-old man presents with pain in the left foot. The patient s foot is red and swollen, and he is unable to bear weight on it. He has had similar past episodes involving the big toe of the right foot and the right elbow that were alleviated with naproxen. He has hypertension, type 2 diabetes, and moderate chronic kidney disease (CKD). Physical examination reveals warmth and redness in the left first metatarsophalangeal joint, which is exquisitely tender. He has nodules over both elbows. How should the patient be evaluated and treated?

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THE CLINICAL PROBLEM

Gout is a chronic disease of monosodium urate deposition characterized by arthritis flares and disability. Lasting days to weeks if untreated, flares are inflammatory, often intensely painful, and debilitating. Separated by asymptomatic intercritical periods, flares can increase in frequency and severity over time. Advanced disease develops in approximately 15% of patients[1] and is characterized by subcutaneous nodules composed of monosodium urate (tophi), unremitting articular inflammation, and potential joint erosion and deformity. Although reports suggest a plateauing of incidence in some geographic regions, the worldwide burden of gout has grown in recent decades.[2] In the United States, gout has been diagnosed in more than 10 million adults,[3] which has contributed to increases in gout-related ambulatory visits and hospitalizations.[4,5]

Hyperuricemia is a necessary but insufficient risk factor. This condition, which is defined as a circulating uric acid level that exceeds the solubility threshold for monosodium urate (>6.8 mg per deciliter), is three to five times as common as gout.[3] The heritability of the serum urate concentration may be as high as 60%[6]; other risk factors for hyperuricemia and gout include male sex, older age, dietary and lifestyle factors, obesity, renal impairment, and the use of medications (e.g., diuretics) that increase urate concentrations.[7]

Gout burden has been magnified during both the coronavirus disease 2019 (Covid-19) pandemic and the opioid epidemic. A study of data from the UK Biobank showed that patients with gout were at a higher risk for infection and death from Covid-19, a hazard partially driven by greater frequency of coexisting disease.[8] Opiates are frequently prescribed to patients during flares,[9] and opiate use is increasingly common. Data showed that hospitalizations from opioid use disorder among persons with gout grew by a factor of more than 36 between 1998 and 2014.[10]

Adding to this burden, gout-related health disparities are pervasive in underrepresented and underserved communities, notably among Black, Pacific Islander, and New Zealand Maori populations.[11,12] Other populations (e.g., Americans of Japanese descent) also have a higher incidence of gout and may have worse out-

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KEY CLINICAL POINTS

GOUT

- Although the presence of monosodium urate crystals in aspirates obtained from joints, bursa, or tophi remains the reference standard, a clinical diagnosis of gout can be made on the basis of the presence of suggestive clinical features.
- When feasible, patients should keep medication on hand (the pill-in-a-pocket approach) to facilitate early antiinflammatory treatment of gout flares.
- Allopurinol represents the first line of therapy to lower urate concentrations and should be administered according to a treat-to-target approach (initial low doses followed by gradual dose escalation) to establish and maintain serum urate concentrations below 6.0 mg per deciliter.
- Treatment for gout must be individualized to account for coexisting cardiometabolic and renal conditions, which are often overrepresented in this patient population.
- Although potentially beneficial in the management of associated conditions, dietary and lifestyle modifications alone are seldom adequate interventions for lowering urate concentrations.

comes. As compared with men, women with gout are less likely to receive appropriate treatment for the condition,[3] more often have hypertension and CKD, and are more likely to have atypical joint involvement that could lead to diagnostic delays.[13]

STRATEGIES AND EVIDENCE

EVALUATION

Patients typically present with an acute flare. Characteristic features of flare include monoarticular involvement of the foot especially the first metatarsophalangeal joint (Fig. 1A) or ankle along with a history of similar episodes, rapid onset or escalation of pain or swelling (or both), erythema, associated coexisting conditions, and hyperuricemia (Table 1). In patients who have had untreated disease for a long period of time but have not yet received a diagnosis, tophi may be present, most often detected over the extensor surface of the elbow or other joint areas.

The European League against Rheumatism (EULAR) has provided a framework for patient evaluation, calling for an approach centered on the identification of monosodium urate crystals in aspirates of synovial fluids or tophi (Fig. 1B).[14] A positive result on polarized microscopy yields 100% specificity and is diagnostic in patients who present with suggestive symptoms and signs.[15] Joint aspiration and other targeted testing procedures are critical to rule out mimics that occur in isolation or with gout, such as septic arthritis or pseudogout (Table 2).

In circumstances in which necessary equipment or technical skills are not available, a diagnosis can be made on the basis of suggestive clinical features (Table 1) and diagnostic algorithms (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[16,17] With persistent diagnostic uncertainty, imaging may be informative. Conventional radiography, most often targeting symptomatic joints in the feet or hands, may show bony erosions of advanced gout characterized by overhanging edges and sclerotic margins. Advanced imaging with musculoskeletal ultrasonography and dual-energy computed tomography can be used as noninvasive techniques to identify monosodium urate deposition (Fig. 1C and 1D),[18,19] although both methods require technical expertise and lack sensitivity in early gout.

Although hyperuricemia is a causal risk factor for gout, serum urate measurement has a limited role in diagnosis owing to low specificity. In a participant-level meta-analysis, most asymptomatic patients with marked hyperuricemia (serum urate concentration, >10 mg per deciliter) were not found to have gout over 15 years of follow-up.[20] Likewise, the negative predictive value of normal serum urate concentrations during a flare is limited, perhaps owing to the urate-lowering effects of inflammation.[21] Important to interpretation is the fact that many clinical laboratories use serum urate reference ranges that are based on population distributions rather than physiological relevance, and concentrations exceeding the monosodium urate saturation point are often deemed normal. Although a single measure is of limited value, persistently normal serum urate concentrations with serial testing in the absence of urate-lowering therapy strongly suggests a diagnosis other than gout.

Other tenets of evaluation include the systematic assessment for coexisting conditions and modifiable risk factors for hyperuricemia.[14] Hyper-

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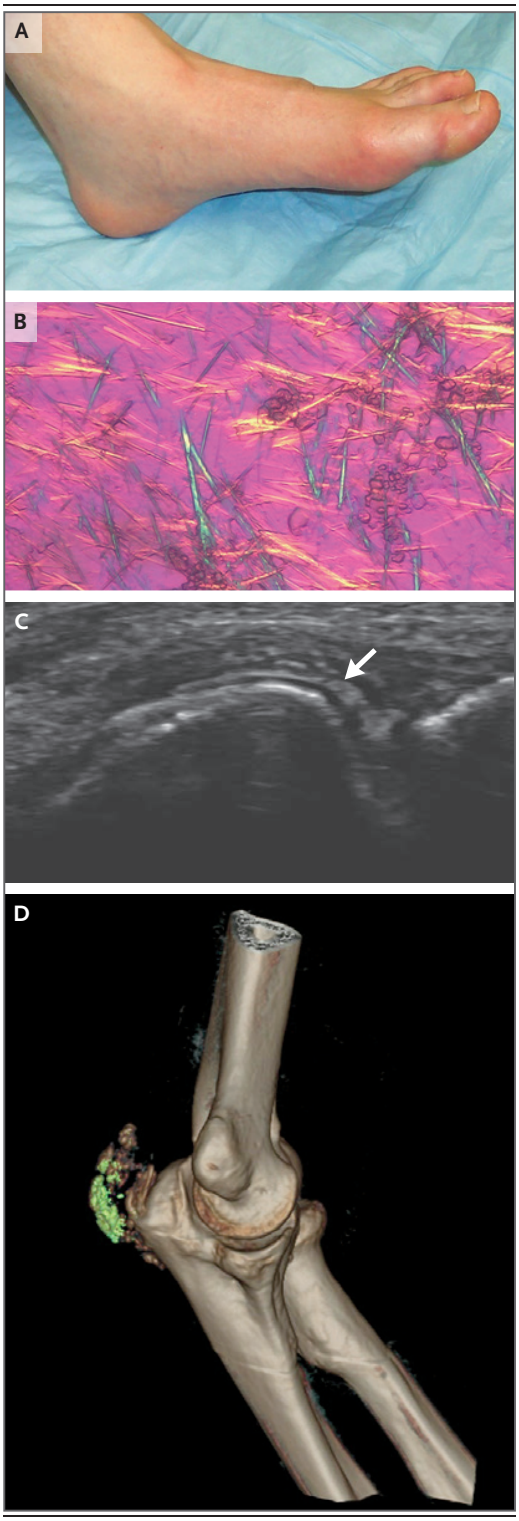

Figure 1. Clinical Findings in Gout.

Shown are findings that include a photograph of gouty arthritis involving the first metatarsophalangeal (podagra) and interphalangeal joints (Panel A); monosodium urate crystals (Panel B) viewed on high-power polarizing light microscopy with first-order red compensator (a plane of red light that extends horizontally, confirming negative birefringence); a musculoskeletal ultrasound image of the first metatarsophalangeal joint (Panel C) that shows the characteristic double-contour sign (arrow) owing to monosodium urate deposition over hyaline cartilage; and dual-energy computed tomography of the elbow (Panel D) that reveals monosodium urate deposition (tophus).

tension, obesity, cardiovascular disease, diabetes, and CKD are all more frequent in persons with gout[22] and collectively help to explain the increased mortality that accompanies this condition.[23]

TREATMENT

FLARE MANAGEMENT

Flares are treated with the goal of rapid pain resolution and restoration of function. Recommended first-line therapies should be individualized on the basis of coexisting conditions and include colchicine, nonsteroidal antiinflammatory drugs (NSAIDs), and glucocorticoids, the latter administered orally, parenterally, or by intraarticular injection (Table 3).[24-26] To expedite treatment, subspecialty guidelines recommend that patients keep medication readily available (the so-called pill-in-a-pocket approach) to take when initial symptoms occur.[24,25] Other agents that are used less commonly in the treatment of flares are shown in Table 3.

On the basis of the key role that nucleotide-binding oligomerization domain like receptor protein 3 (NLRP3) plays in gout-related inflammation, including the activation and release of interleukin-1, colchicine is used to block NLRP3 oligomerization. Of the recommended first-line options, parenteral glucocorticoids may offer the most rapid pain relief.[26] Although corticotropin and inhibitors of interleukin-1 represent potentially efficacious options, these approaches are limited by cost and availability.

URATE-LOWERING THERAPY

Allopurinol, a xanthine oxidase inhibitor available since the 1960s, remains the first-line urate-lowering therapy (Table 3). Other options include febuxostat (a xanthine oxidase inhibitor), probenecid (a uricosuric), benzbromarone (a uricosuric not available in the United States), and less commonly, pegloticase. In the randomized,

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Table 1. Characteristic Clinical Features Suggestive of Gout Flare.

Monoarticular joint involvement, especially involving the first metatarsophalangeal joint
Rapid onset and escalation of symptoms (often reaching maximum intensity in ≤24 hours)
Erythema overlying the joint
Inability to tolerate pressure or palpation of the joint; inability to bear weight or use the joint
Similar previous episodes of arthritis that spontaneously resolved
Male sex
Hyperuricemia or use of medications causing hyperuricemia (e.g., diuretics or low-dose aspirin)
Cardiometabolic disease or renal insufficiency
Subcutaneous nodules consistent with tophi

double-blind STOP Gout trial, allopurinol (at a dose of up to 800 mg per day) was noninferior to febuxostat (at a dose of up to 80 to 120 mg per day) for flare prevention and lowering of urate; 81% of patients who received allopurinol and 78% who received febuxostat reached target serum urate concentrations at 48 weeks.[1] If therapy with recommended doses of allopurinol and febuxostat fails, other treatment options include a uricosuric alone or in combination with a xanthine oxidase inhibitor. Data from randomized, controlled trials suggest that among uricosurics, benzbromarone may be superior to probenecid. Among patients in whom allopurinol was ineffective or caused unacceptable side effects, 92% of those who received benzbromarone at a dose of 200 mg per day reached serum urate levels of less than 5.0 mg per deciliter after 2 months of treatment, as compared with 65% of those who received probenecid at a dose of 2000 mg per day.[27] The results of replicate randomized, controlled studies suggest that intravenous pegloticase represents an alternative,[28] although its use may be complicated by the formation of anti-pegloticase antibodies leading to infusion reactions and efficacy loss; small studies have shown that treatment durability is improved by the coadministration of immunosuppressants such as methotrexate and mycophenolate mofetil.[29,30]

The guidelines of subspecialty societies recommend a treat-to-target approach[24,25] characterized by the initiation of low-dose urate-lowering therapy with gradual adjustment to reach and maintain serum urate concentrations of less than 6.0 mg per deciliter. In contrast, the American College of Physicians, citing a lack of robust evidence to support this approach, advocates for a treat-to-avoid-symptoms strategy.[31] However, in the absence of guidance on how best to avoid symptoms, the application of this recommendation is problematic. The treat-to-avoid-symptoms approach could include treatment strategies that do not address the primary problem of monosodium urate deposition, such as the long-term use of colchicine, NSAIDs, or glucocorticoids in the absence of urate-lowering therapy. Since the American College of Physicians released its treat-to-avoid-symptoms guidance, additional evidence supporting a treat-to-target approach has emerged, including a trial that assessed a nurse-led intervention in which a treat-to-target urate-lowering therapy led to reductions in flare frequency and tophi (Table S2).[32] At 2 years, only 8% of patients who received treat-to-target urate-lowering therapy had more than two flares annually, as compared with 24% of those who received usual care.

Indications for urate-lowering therapy for the treatment of gout include recurrent flares (e.g., ≥2 per year), the presence of tophi, and evidence of gout-related joint damage with erosive changes shown on radiographs. Although these indications are common in established gout, several studies and resulting guidance recognize the potential for even earlier intervention, particularly among patients with marked hyperuricemia, renal stones, or CKD.[24,25,33] Accordingly, European guidelines recommend that urate-lowering therapy be considered and discussed with all patients with gout from the time of initial presentation with gout.[25]

Because flares may occur as a physiologic consequence of rapid lowering of urate levels, best practices include the use of antiinflammatory prophylaxis during the initiation and adjustment phases of urate-lowering therapy. An alternative approach is stepwise initiation of urate-lowering therapy. An open-label, randomized trial showed that stepwise initiation of febuxostat at a dose of 10 mg per day followed by gradual dose escalation was similarly as effective in preventing flares as daily colchicine given concomitantly with febuxostat at a dose of 40 mg per day.[34]

GOUT THERAPIES AND COEXISTING CONDITIONS

The presence of coexisting conditions complicates the management of gout. Therapies for

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gout affect the status of coexisting conditions or may interact with medications that are used to manage these conditions. For example, hypertension is observed in approximately 75% of patients with gout[22] and can be exacerbated by receipt of NSAIDs or glucocorticoids (Fig. 2). Conversely, longer-term use of colchicine and canakinumab (an interleukin-1β inhibitor) provides cardiovascular protection in patients who do not have gout.[35,36] Whether the recurrent, limited, or long-term use of these agents that are typical in the management of flares or as prophylaxis provides similar protection to patients who have gout is unknown.

Although previous guidance recommended low and fixed doses of allopurinol in the treatment of patients with CKD, recent reports support the extension of treat-to-target use of allopurinol to this population. Among patients with CKD in the STOP Gout trial, the efficacy and safety of allopurinol and febuxostat were similar.[1] The initiation and dose escalation of allopurinol and the resulting serum urate goal in patients who have gout and concurrent moderate-to-severe CKD have not been linked to worsening renal function or to reduced survival.[37] Allopurinol hypersensitivity syndrome represents a rare but potentially life-threatening treatment complication that is characterized by severe cutaneous eruptions, eosinophilia, and acute hepatic and renal injury. The risk of allopurinol hypersensitivity syndrome is increased in patients with CKD. Testing for the HLA-B*5801 risk allele enables stratification for risk and appears to be cost-effective in Asian patients and Black patients of African ancestry (independent of their CKD status), in whom inheritance of this gene is more common.[38]

EFFECTS ON GOUT FROM TREATMENT OF COEXISTING CONDITIONS

Just as gout therapies can affect patients coexisting conditions, treatment of those conditions can affect gout (Fig. 2). A well-known example is that diuretics increase serum urate concentrations. Patients who receive beta-blockers, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers other than losartan are at increased risk for gout.[39] Conversely, losartan, calcium-channel blockers, fenofibrate, and sodium glucose transport protein 2 (SGLT2) inhibitors promote uricosuria and lower serum urate concentrations. A meta-analysis that pooled 62 studies of different SGLT2 inhibitors showed a mean reduction in serum urate concentrations of 0.6 mg per deciliter in follow-up over 4 to 206 weeks, one of several biologic effects that is

Table 2. Distinguishing Clinical Features of Common Gout Mimics.*

Differential Diagnosis	Clinical Findings Suggestive of Other Diagnosis
Gout flare	
Pseudogout from CPPD	Symptoms associated with hyperparathyroidism, hypothyroidism, hemochromatosis, and hypomagnesemia
	CPPD crystals in synovial fluid (rhomboidal morphology and weak or positive birefringence)
	Articular chondrocalcinosis shown on radiograph
Septic arthritis	Prosthetic joint involvement
	Prominent systemic symptoms (e.g., temperature >38.5 C, rigors, and chills)
	Evidence of distant infection (e.g., bacteremia and endocarditis)
	Marked synovial leukocytosis (e.g., white-cell count >50,000 cells per ml)
	Positive synovial Gram s stain or culture
Trauma	Preceding trauma or injury
	Imaging reveals trauma (e.g., stress fracture)
Cellulitis	Cutaneous erythema distant from joint
Osteoarthritis	Insidious onset, chronic course
	Absent or minimal inflammation on exam
	Noninflammatory synovial fluid
	Characteristic imaging findings (e.g., asymmetric joint space loss, subchondral sclerosis, or osteophytes)
Palindromic rheumatism	Rheumatoid factor, anti-CCP antibody positivity
Tophaceous gout	
Osteomyelitis	Persistent, marked elevations in ESR or CRP
	Positive bacterial tissue or bone cultures
Rheumatoid arthritis	Insidious onset, chronic course
	Subcutaneous nodules associated with chronic, symmetric arthritis of small joints
	Rheumatoid factor, anti-CCP antibody positivity
	Presence of other extraarticular features (e.g., interstitial lung disease and Felty s syndrome)
Dactylitis	
From reactive arthritis	Preceding dysentery or sexually transmitted disease; presence of sacroiliitis, conjunctivitis, urethritis, keratoderma blennorrhagicum, or circinate balanitis
From psoriatic arthritis	Presence of skin psoriasis, nail pitting or onycholysis, or sacroiliitis

* CCP denotes cyclic citrullinated peptide, CPPD calcium pyrophosphate deposition disease, CRP C-reactive protein, and ESR erythrocyte sedimentation rate. These conditions may coexist with hyperuricemia and gout.

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Table 3. Therapies Used in the Management of Gout.*

Therapy	Dose	Contraindications
First-line agents for flare management and prophylaxis		
Colchicine		Hepatic cirrhosis or severe chronic kidney disease (eGFR of <20 to 30 ml/min), concomitant use of drugs that strongly inhibit cytochrome P450 3A4 or P-glycoprotein (e.g., clarithromycin)
Flare	1.0 to 1.2 mg administered orally followed by 0.5 to 0.6 mg administered orally after 1 hour on day 1; then 0.5 to 0.6 mg administered orally once or twice daily for 7 to 10 days starting on day 2	
Prophylaxis	0.5 to 0.6 mg administered orally once or twice daily	
Glucocorticoids		Poorly controlled diabetes mellitus, active infection
Flare	Initial dose of 0.5 mg/kg of body weight per day (administered orally or intravenously) prednisone equivalent, followed by gradual taper over 7 to 10 days	
Prophylaxis	5 to 10 mg daily prednisone equivalent	
NSAIDs		Peptic ulcer disease, chronic kidney disease, severe cardiovascular disease, concomitant anticoagulation therapy, hypersensitivity to salicylates
Flare	Full antiinflammatory doses (e.g., diclofenac 50 mg administered orally twice daily) for 7 to 10 days	
Prophylaxis	Low dose (e.g., naproxen 220 to 250 mg administered orally twice daily)	
Alternative agents for flare management		
Interleukin-1 inhibitor		Active infection
Anakinra	100 mg per day administered subcutaneously	
Canakinumab	150 mg administered subcutaneously in a single dose	
Rilonacept	160 to 320 mg administered subcutaneously in a single dose	
Corticotropin	40 IU administered subcutaneously in a single dose	Poorly controlled diabetes mellitus, active infection
First-line urate-lowering agent		
Allopurinol	Initial dose of ≤100 mg administered orally daily; gradual adjustment up to 800 to 900 mg administered orally daily	Allopurinol hypersensitivity, concomitant use of azathioprine or mercaptopurine, positivity for at least one HLA:5801 risk allele
Alternative urate-lowering agents		
Febuxostat	Initial dose of 40 mg administered orally daily; gradual adjustment up to 80 to 120 mg administered orally daily	Concomitant use of azathioprine or mercaptopurine
Uricosuric		Blood dyscrasias, nephrolithiasis, active peptic ulcer disease
Benzbromarone	Initial dose of 50 mg administered orally daily adjusted to maximum daily dose of 200 mg administered orally	
Probenecid	Initial dose of 250 to 500 mg twice a day adjusted to maximum cumulative daily dose of 2000 mg daily	Active peptic ulcer disease

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Table 3. (Continued.)

Therapy	Dose	Contraindications
Pegloticase	8 mg administered intravenously every 2 weeks; consider use of concomitant immunosuppression with weekly methotrexate or mycophenolate mofetil	Known allergy to pegloticase or its components, previous exposure with loss of efficacy (pre-infusion serum urate >6 mg/dl), concomitant receipt of other urate-lowering drugs

* The abbreviation eGFR denotes estimated glomerular filtration rate, and NSAID nonsteroidal antiinflammatory drug.
For severe flare, colchicine may be used in combination with NSAIDs or glucocorticoids; glucocorticoids may also be administered by intra-articular injection; the appropriate dose of prophylaxis is not well defined for interleukin-1 inhibitors or corticotropin; a network meta-analysis has shown that acetic acid derivative NSAIDs (e.g., indomethacin or diclofenac) may have better efficacy in flare than propionic acid derivatives (e.g., ibuprofen or naproxen).[26]
The use of the interleukin-1 inhibitors anakinra and canakinumab for the treatment of gout is not approved by the Food and Drug Administration but is approved by the European Medicines Agency.
Allopurinol and febuxostat inhibit xanthine oxidase; pegloticase is a recombinant uricase that metabolizes uric acid into allantoin (approved for treatment-refractory gout). Uricosurics may lack efficacy with advanced renal impairment. The American College of Rheumatology conditionally recommends HLA:5801 testing before starting allopurinol in patients of Southeast Asian descent and Black patients of African descent, regardless of renal function.[24] Benzbromarone is not available in the United States.

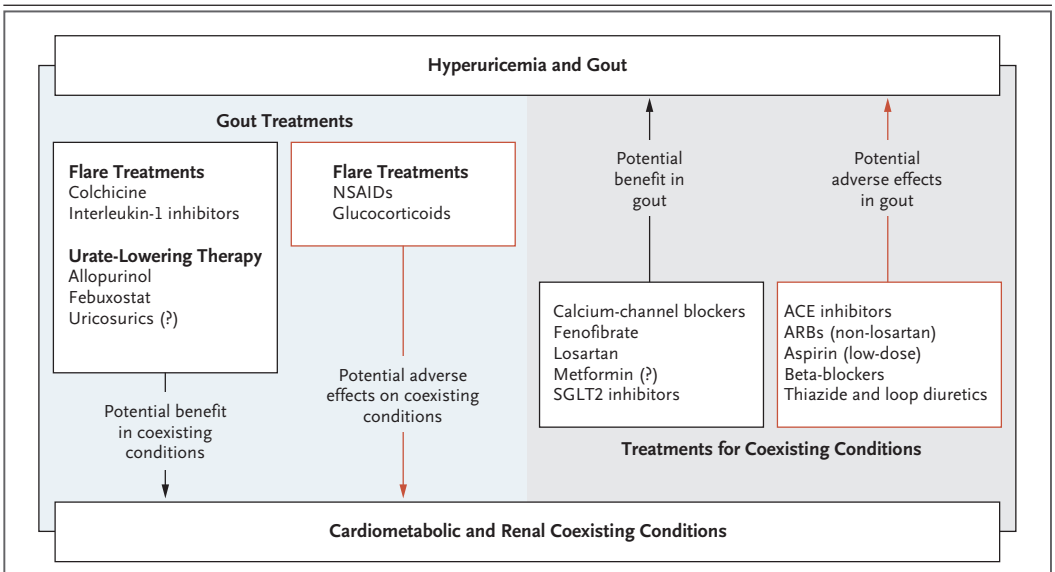

Figure 2. Potential for Dual Benefit or Adverse Effects Associated with Medications Used in Gout and Gout-Related Conditions.

ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, NSAID nonsteroidal antiinflammatory drug, and SGLT2 sodium glucose transport protein 2. Colchicine should be used with caution if agents that strongly inhibit both cytochrome P450 3A4 and P-glycoprotein (e.g., itraconazole and clarithromycin) are used concurrently. A question mark in parentheses indicates that the potential benefit of the agent is less well established.

potentially relevant in gout.[40] Metformin, commonly used in the treatment of patients with type 2 diabetes, can attenuate cellular inflammation triggered by monosodium urate crystals and may reduce flare burden.[41] Collectively, data suggest that the pleiotropic effects of some treatments for coexisting conditions may improve outcomes in gout.

DIET AND LIFESTYLE MODIFICATIONS

Modifiable lifestyle or dietary factors that adversely affect serum urate levels and flare risk include alcohol use (especially beer), dehydration, obesity, and consumption of high-fructose sweeteners (e.g., nondiet sodas) and high-purine foods (e.g., meats and shellfish).[7] Although epidemiologic studies have linked dietary factors

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and obesity with gout risk, the efficacy of dietary and lifestyle interventions in management of gout has been the subject of limited study, with available data suggesting only modest benefit. A 2019 systematic review that included data from 18 clinical trials of dietary interventions (e.g., low-calorie, low-purine diets) showed urate-lowering effects that were generally small in magnitude (<1 mg per deciliter). The risk of bias in the pooled studies was universally moderate-to-high. Study heterogeneity precluded formal meta-analysis.[42]

PATIENT EDUCATION AND ENGAGEMENT

Pervasive misconceptions of gout as self-inflicted and nonserious serve as barriers to management and are shared by patients and providers.[43] Despite the availability of inexpensive and effective therapies, gaps in care persist. Although gout is a lifelong condition, more than half of patients discontinue urate-lowering therapy within 1 year after initiation.[44] However, low adherence to treatment may be overcome with education and close follow-up of patients. In a randomized, controlled trial that examined a nurse-led intervention that combined urate-lowering therapy with education and engagement of patients,[32] adherence to urate-lowering therapy after 2 years was 96% in the intervention group as compared with 56% in the control group (usual care).

Collectively, interventions led by nurses and pharmacists have been associated not only with improved engagement with patients but also with greater adherence to treatment and a higher likelihood of meeting treatment goals.[45] Recent guidelines have conditionally recommended the administration of urate-lowering therapy by nonphysician providers as part of a care model that includes patient education and shared decision making.[24]

AREAS OF UNCERTAINTY

Uncertainties remain with regard to the management of gout.[24,25] These uncertainties include the appropriate serum urate threshold for patients with advanced disease; potential adverse effects of prolonged and profound urate-lowering therapy (e.g., serum urate, <3 mg per deciliter), since epidemiologic studies have identified inverse associations between serum urate concentrations and the risk of neurodegenerative conditions[46]; the correct duration of antiinflammatory prophylaxis after the initiation of urate-lowering therapy; and the appropriate means of improving urate-lowering therapy uptake and adherence.

Convincing evidence that supports a causal role of serum urate in conditions other than gout and nephrolithiasis is lacking.[47] Findings from a randomized, controlled trial suggested that allopurinol improved endothelial function,[48] so urate-lowering therapy could conceivably provide protection against coexisting cardiovascular conditions by mechanisms that are as yet unknown and independent of urate-lowering properties.

On the other hand, the Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial, which was conducted after the Food and Drug Administration (FDA) ordered cardiovascular safety assessments of febuxostat in patients with gout and cardiovascular disease, aroused safety concerns with regard to urate-lowering therapy.[49] The 2018 trial showed that cardiovascular-related mortality and all-cause mortality were higher among patients who were randomly assigned to receive febuxostat than among those who received allopurinol, which prompted an FDA black-box warning for febuxostat. Since that time, the Febuxostat versus Allopurinol Streamlined Trial (FAST) showed no treatment differences in the occurrence of cardiovascular events, including deaths from cardiovascular causes or death from any cause.[50] These studies included different methods with respect to the use of blinding, the proportion of participants with cardiovascular disease, the composite outcomes that were examined, and the follow-up strategies that were used, among other differences.[51] Problems with the CARES trial (including a loss to follow-up approaching 50%) and reassuring findings from FAST (which had a 5.8% loss to follow-up) have led experts to call for the FDA to reconsider its warning with regard to febuxostat.[52]

GUIDELINES

Published reviews have summarized guidelines for the management of gout.[53,54] Other recent

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summaries highlight discrepancies between guidance documents from subspecialty societies that favor treat-to-target urate-lowering therapy and the American College of Physicians guidelines that endorse a treat-to-avoid-symptoms approach.[31] Recommendations presented here are generally consistent with subspecialty guidance.[24,25]

CONCLUSIONS AND RECOMMENDATIONS

The presentation of the patient described in the vignette is characteristic of gout. If feasible, and particularly if not previously done, a diagnosis of gout should be confirmed. In this case, confirmation could be accomplished by means of aspiration of the first metatarsophalangeal joint or suspected tophi, with monosodium urate crystals revealed under polarized microscopy. A careful history is essential to identify other conditions and medications that could affect care. To alleviate flare symptoms, options would include low-dose colchicine (≤1.8 mg per day for a total of 7 to 10 days) or intraarticular glucocorticoids; both NSAIDs and systemic glucocorticoids should be avoided owing to coexisting conditions. On the basis of indications of recurrent flare and tophi, low-dose allopurinol should be initiated either concurrently during treatment of the flare with antiinflammatory agents or after symptoms have resolved. Antiinflammatory prophylaxis (e.g., colchicine at a dose of 0.5 to 0.6 mg per day) should be used during initiation of urate-lowering therapy and adjustment of the dose. Allopurinol dose levels should be gradually increased (e.g., every 3 to 6 weeks) on the basis of serum urate measurements at regular intervals to avoid therapeutic inertia and to reach and maintain the serum urate concentration at less than 6.0 mg per deciliter. Antiinflammatory prophylaxis should be stopped after the serum urate target has been met and the patient is flare-free for a period of at least 1 month. The education and engagement of patients, which can be facilitated through nonphysician providers, should be conducted over the course of clinical encounters with a focus on factors that confer a predisposition to gout flares and the role of urate-lowering therapy in reducing the risk of flares. Patients should also be educated about lifestyle and dietary interventions, although the effects of these are generally modest.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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