Continuing Medical Education

Evolving Concepts in Gout Diagnosis and Treatment

Here's the latest update on this most common inflammatory condition.

Objectives

1) To examine the significant role of uric acid as a factor in the pathogenesis of gout.

2) To understand similarities and differences in the clinical presentations of an acute attack of gout and chronic gout disease.

3) To identify both non-pharmacological lifestyle interventions and traditional and newer pharmacological interventions for the treatment of all presentations of gout.

4) To educate patients on medication adherence and commitment to treatment in the successful management of gout.

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*Following this article, an answer sheet and full set of instructions are provided (p. 190).—**Editor***

By Robert G. Smith DPM, MSc, RPh

Gout is the most common inflammatory arthritis in the United States with three to five million afflicted individuals.[1,2] It has been reported that both the incidence and the prevalence of gout appear to be increasing worldwide.[3] Gout is perhaps the oldest known type of arthritis, colorfully depicted in art and literature along with commentaries on the moral character of the gout sufferer (Figure 1). Literary accounts have referred to gout's association with rich foods and excessive alcohol

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consumption—thus the description "the disease of kings."

Gout is a monosodium urate monohydrate crystal deposit disease with a very rich history that mirrors the evolution of medicine itself.[4,5] Hippocrates noted the link between gout and an intemperate lifestyle. He referred to podagra as an "arthritis of the rich."[5] Antoni van Leeuwenhoek was the first to describe the appearance of the crystals from a gouty tophus.[5]

Many years later, McCarty and Hollander described, in their classic report, the use of compensated polarized light microscopy to identify monosodium urate crystals as the cause of gout during an examination of synovial fluid.[5] Seegmiller and colleagues described the relative roles of excessive urate production and impaired excretion in the pathogenesis of hyperuricemia.[5] Because gout has been recognized for so many centuries, its diagnosis and treatment have not elicited much interest; thus, the management of gout remains a challenge for the clinician caring for a gout patient.[6]

Recent medical literature recognizes that most patients with gout visit a primary care physician for disease management, and there are challenges to diagnosing and treating gout in this setting.[7] Weaver, et al. stated that the arrival of newer investigational agents on the market has prompted rheumatologists to consider how they can share current information to improve gout management.[7]

It is this concept of sharing current information from clinical-based medicine as described in recent published reviews on the management of gout[6-9] that is the main impetus for the preparation of this review. It is hoped that, empowered with this knowledge, the prescribing clinician can improve patient outcomes when treating gout. First, new insights into the pathogenesis of hyperuricemia and gout will be discussed. Second, risk factors, typical presentations of symptoms, and key diagnostic parameters will be reviewed.

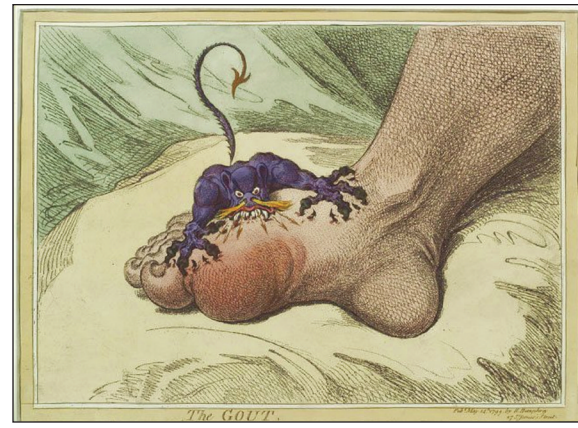

Figure 1: The Gout (1799), by the artist James Gilray, depicts gout as an evil demon attacking a toe (Published by Hannah Humphrey-May 14,1799).

Uric acid, the most insoluble of the purine substances, is a trioxypurine containing three oxygen groups.

Finally, nonpharmacologic treatment modalities and current, as well as newer investigational therapeutics, will be offered to assist podiatric physicians with the aim of achieving greater patient adherence through medication counseling.

Pathogenesis

Hyperuricemia is a common serum abnormality that sometimes progresses into gout. Biologically significant hyperuricemia occurs when serum urate levels exceed solubility (~6.8 mg/dL). Humans generate about 250 to 750 mg of uric acid per day; the uric acid comes from dietary purines and the breakdown of dying tissues.

The exact cause of gout is not yet known, although it may be linked to a genetic defect in purine metabolism. Uric acid, the most insoluble of the purine substances, is a trioxypurine containing three oxygen groups. The pathogenesis of gout begins with the crystallization of urate within the joint, bursa, or tendon sheath, which leads to inflammation as a result of phagocytosis of monosodium urate crystals; it is usually associated with an elevated concentration of uric acid in the blood.[2,9]

Specifically, uric acid is a breakdown product of the purines adenine, guanine, hypoxanthine, and xanthine. Adenine and guanine are found in both DNA and RNA; hypoxanthine and xanthine are not incorporated into the nucleic acids as they are being synthesized, but they are important intermediates in the synthesis and degradation of the purine nucleotides. Undissociated uric acid and monosodium salt, which is the primary form found in the blood, are only sparingly soluble.

The amount of urate in the body depends on the balance between dietary intake, synthesis, and excretion.[10] In patients with primary gout, defects in purine metabolism cause hyperuricemia or high levels of uric acid in the blood. This can be caused through an over-production and/or an under-excretion of uric acid. Hyperuricemia results from the over-production of urate found in 10% of gout patients and from under-excretion of urate found in the remaining 90%.[10]

The majority of patients with endogenous over-production of urate have the condition as a result of salvaged purines arising from increased cell turnover in proliferation and inflammatory disorders, from pharmacologic intervention resulting in increased urate production, and from tissue hypoxia.[10]

Renal Mechanism

The renal mechanism for handling urate is one of glomerular filtration followed by partial tubular reabsorption.[11] The final fractional excretion of uric acid is about 20% of what was originally filtered. Uric acid levels independently predict renal failure in patients with preexisting renal disease.

Hyperuricemia causes interstitial and glomerular changes that are independent of the presence of

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crystals, and the changes very much resemble what hypertensive changes would look like chronically. In addition, serum hyperuricemia is epidemiologically linked to hypertension and seems to be an independent factor for the development of hypertension.

Serum uric acid can be normal, especially during the gout attack. The target goal for uric acid treatment is maintaining a level less than 6.0 mg/dL.

Risk Factors for Gout

A number of references by Choi et al. have discussed risk factors for the development of gout.[12-15] Nonmodifiable risk factors include being a male or a post-menopausal female, genetic influences, end-stage renal disease, and the resultant major organ transplantation. Its prevalence increases with age, from 1.8/1,000 in people under the age of 45 years to 30.8/1,000 with those over age 65.[8,9]

Elevated serum urate levels are also associated with increased risk.[8,9] Hypertension is a definite risk factor, as a significant percentage of patients with hyperuricemia will develop hypertension. Hyperuricemia and gout have been linked to other disease states including metabolic syndrome, cardiac disease, stroke, and renal disease.[8,9] The risk of gout correlates with truncal obesity, as measured by body mass index and waist-to-hip ratios.[8,9,12]

Avoidable risk factors include diet and medications. Foods that have been implicated in causing gout are red organ meats, seafood, and foods containing high-fructose corn syrup. Fructose has been recognized as a cause of hyperuricemia.[8,9,15-17] Choi, et al. conducted a small prospective study that investigated the tendency of diets high in fructose to induce higher serum urate levels relative to diets high in glucose or low in carbonates.[17] High alcohol intake, especially of beer, is also a risk factor: the presence of guanosine in beer has been identified as a cause of gouty attacks.

Certain drugs used to treat gout, particularly thiazide diuretics and the use of cyclosporine in transplant patients, have been implicated in gouty attacks. Despite the cardio-preventive benefit of taking low doses (81 mg) of aspirin, aspirin itself may be associated with the onset of gout.[8,9,18] The use of cyclosporine has been commonly reported to cause a rapid-onset type of gout that is swiftly ascending and polyarticular in many cases.

Roubenoff confirms that these risk factors are increasing, reporting that gout incidence and prevalence have increased by two-fold from 1970 to 1990.19 Furthermore, Wallace, et al. reported that the prevalence of gout has increased by two cases per 1,000 patients during the 1990s due to lifestyle changes.[20]

Biologically significant hyperuricemia occurs when serum urate levels exceed solubility (~6.8 mg/dL).

Typical Presentation of Gout

Gouty attacks are usually associated with a precipitating event.[6,8,21] These attacks consist of intense pain involving the lower extremity with 80% of first attacks involving a monoarticular joint. However, after long periods of time, gout attacks may become polyarticular.[6,8,21,22] This pain and inflammation is a result of a dramatic inflammatory response. Some authors have estimated that between 50% to 90% of initial attacks occur in the first metatarsophalangeal joint (podagra).[6,8,22-24]

In postmenopausal women, the distal interphalangeal joints may be involved.[6] Attacks often occur at night and are associated with a precipitating event.[6,8,21] Acute gouty arthritis may be accompanied by low-grade fevers, chills, and malaise.[6,8,22,24] The majority of patients experience a second acute gout attack within one year of the first episode.[24] Untreated initial acute gout attacks resolve completely within 3 to 14 days.[6,21,24]

Clinical Stages

There are four clinical stages of gout.[8,24] At serum urate concentrations greater than 6.8 mg/dL, urate crystals may start to deposit. Hence, the first stage of gout is known as asymptomatic hyperuricemia. During this first period, urate deposits may directly contribute to organ damage.

After sufficient urate deposits have developed around a joint and a traumatic event triggers the release of crystals into the joint space, patient will suffer an acute gout attack and move into the second stage, known as acute gouty arthritis. During this second stage, acute inflammation in the joint (caused by urate crystallization and crystal phagocytosis) is present. This episode is known as a "flare" and is self-resolving and likely to recur.

The interval between acute flare gout attacks with persistent crystals in the joints is the third stage and is known as an intercritical period. When crystal deposits continue to accumulate, patients develop chronically stiff and swollen joints, leading to the final stage, advanced gout, which includes the long-term complications of uncontrolled hyperuricemia characterized by chronic arthritis and tophi.

The nodular mass of uric acid crystals is described as a tophus and, in gout patients, is characteristically deposited in different soft tissue areas of the body. This advanced stage of gout is uncommon because it is avoidable with interventional therapy.[24]

Diagnosis

The diagnosis of gout can be straightforward. The only way to establish a diagnosis of gout with certainty is to test for uric acid crystals in the synovial fluid or tophi.[7] Polarizing microscopic examination of synovial fluid reveals negatively birefringent crystals, which confirms the diagnosis of gout. It should be noted that normal uric acid levels are observed in approximately 50% of acute gouty flares.[7]

Dalbeth's and McQueen's review summarizes recent advances in plain

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radiography and advanced imaging for gout, calcium pyrophosphate dihydrate crystal arthropathy, and basic calcium phosphate crystal arthropathy.[25] They suggest that the use of high-resolution ultrasonography may improve noninvasive diagnosis of the crystal-induced arthropathies and allow for monitoring of intra-articular tophi. They also determined that computed tomography reveals the tophi and bone erosion in high definition and promoted three-dimensional computed tomography to assess tophus volume as a promising diagnostic tool for gout.[25]

Finally, they indicated that magnetic resonance imaging may also be a reliable method for the assessment of tophus size in gout, and that it has an important role in detecting disease complications in clinical practice.

Polarizing microscopic examination of synovial fluid reveals negatively birefringent crystals, which confirms the diagnosis of gout.

Treatment of Gout

Key elements necessary for improving clinical outcomes in gout management include enhancing the education of health professionals and patients, in addition to exploring novel urate-lowering agents. Podiatric clinicians can appreciate that the optimal treatment for gout requires both adjunctive non-pharmacologic as well as pharmacologic interventional therapies (Table 1).[8]

Becker and Chohan recommend implementing the twelve evidence-based recommendations from the European League Against Rheumatism (EULAR) to achieve successful gout management (Table 2).[26,27] Treatment and prevention of acute gout flares, as well as the management of hyperuricemia and gout, can be best achieved using a brief narrative and accentuated graphically, using easy-to-read tables that may be accessed quickly by the podiatric physician when a question arises.

The treatment regimen must be tailored to each patient. The treatment of gout has three main components: therapy for the acute attack, prophylaxis against gout flares, and management of the hyperuricemia.[8,9] Several aspects must be independently considered when planning to treat a patient with gout. Because gout is a reversible urate crystal deposit disease, the main objective is to eliminate the urate crystals from the joints and other structures.[28] Li-Y,u et al. determined, in a 10-year prospective study, that serum urate levels should be reduced below 6.0 mg/dL in order to eliminate crystals.[29]

One key observation for the podiatric physician to understand is that pharmacological agents that treat co-morbidities associated with gout and hyperuricemia may affect serum uric acid levels and may influence treatment approaches to gout management.

Medications and Gout

Many medications exert their effect on serum uric acid levels by influencing uric acid excretion (primarily by the kidneys) specific to renal urate transporters, particularly urate transporter 1 (URAT 1).[12] Pharmacological agents and the resulting effect of serum uric acid levels are summarized in Table 3. Choi, et al. describe mechanisms of actions for a number of these medications and explain how these agents influence serum uric acid levels.[12]

Diuretics increase renal tubular re-absorption associated with volume depletion and may consequently simulate URAT 1.[12] Cyclosporine and tacrolimus both increase renal tubular re-absorption of uric acid, thereby increasing serum uric acid.[12] On the other hand, pyrazinamide, nicotinate, lactate, and acetoacetate increase uric acid levels via trans-stimulation of URAT 1.[12] Low-dose salicylate and etambutol decrease renal urate excretion.[12]

Clinical observations have demonstrated that beta-blockers increase serum uric acid levels but have not identified the exact mechanism of action. A few anti-hypertensive agents decrease serum acid levels. Losartan inhibits URAT 1 and amlodipine increases renal urate excreation. Both probenecid and high-dose salicylates inhibit URAT 1.

Finally, fenofibrate may inhibit URAT 1, while both allopurinol and febuxostat lower serum uric acid levels by inhibiting xanthine oxidase.[12]

Pharmacotherapy for Acute Gout Attacks

Medications used to treat an acute gout attack include non-

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TABLE 1
Adjunctive Therapy for Gout and Associated Co-morbidities[a]

- Control weight with daily exercise.
- Limit consumption of red meat.
- Replace consumption of fish with omega-3 fatty acids.
- Refrain from foods and drinks containing high fructose.
- Consume 1-2 servings of dairy or calcium supplements daily.
- Consume nuts and vegetables daily.
- Supplement diet with vitamin C.
- Consumption of coffee may be beneficial.

[a] *Podiatric physicians are uniquely positioned to counsel the gout patient on both diet and lifestyle changes to create healthy benefits for the prevention and treatment of co-morbidities.*

steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids. A combination of these agents may also be necessary. A summary of the pharmacological agents used to treat acute gout is presented in Table 4.[6-9,26-29] These medications have no effect on the serum uric acid level.

The classic antidote for gouty arthritis is colchicine, an alkaloid derived from autumn crocus (Colchicum autumnale).[5] The most frequent adverse drug event associated with colchicine use is reported to be diarrhea.[6] However, even low-dose colchicine may be associated with severe adverse effects and toxicity such as myopathy and myelosuppression.[6,8,9,28,29] Monitoring serum troponin levels during an acute colchicine overdose may help prevent vascular collapse.[30]

Guidelines indicate that fast-acting oral NSAIDs should be used during acute attacks if there are no contraindications.[6-9,27] As there are no significant clinical differences among NSAIDs, the choice of agent should be based on the agent's side-effect profile, cost, and the patient's ability to adhere to the prescribed agent.[6,8,9,26,28] Suppressive therapy to prevent flares usually involves colchicine or NSAIDs.[8,9]

An important factor in choosing therapeutic agents for an acute attack is the presence of co-morbidities. The most common therapy for acute gout, in the case of acute, or chronic renal, or hepatic failure, is corticosteroids.[8,9] If NSAIDs and colchicine are contraindicated due to patient co-morbidities, intra-articular aspiration and the injection of a corticosteroid is an effective treatment for an acute attack of gout, after the possibility of a septic joint has been eliminated.[6]

Urate-Lowering Therapy

The therapeutic goal of urate-lowering therapy is to promote dissolution of urate crystals and to prevent crystal formation.[6,8,29] In addition, urate-lowering therapy is used to prevent disease progression, reduce the frequency of acute attacks, and maintain and improve the patient's quality of life. Treatments for chronic gout are aimed at reducing serum urate levels to less than 6.0 mg/dL in order to dissolve existing crystals and prevent the formation of new ones.[8,9]

Dore recommends that patients who overproduce urate be treated with allopurinol, as this drug has the advantage of being effective for both over-producers and under-excretors.[6] Patients who under-excrete urate, despite having near-normal creatinine clearance levels, should be treated with uricosurics. Urate-lowering therapy should be life-long.

If an acute flare occurs when urate-lowering therapy is initiated, therapy should not be discontinued as this will result in fluctuating urate levels.[31] Initiating urate-lowering therapy can mobilize urate deposits, which may precipitate an attack due to rapid serum uric acid lowering.[7]

The practice of using concomitant gastro-protectant NSAID and colchicine prophylaxis with the initialization of urate-lowering therapy has been suggested.[7,26] Podiatric physicians, as experts in the lower extremities can be a tremendous resource by informing the other

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TABLE 2
Summary of Twelve Recommendations for Gout Management from EULAR
(Modified for the U.S.)

1) Utilize both non-pharmacologic and pharmacologic modalities tailored to risk factors.
2) Stress patient education and lifestyle changes (weight loss and alcohol reduction).
3) Address patient's co-morbidities such as hypertension, hyperglycemia, hyperlipidemia, obesity, and smoking.
4) Oral colchicine and/or NSAIDs are first-line agents for systemic treatment of acute attacks.
5) Low doses of colchicine may be sufficient for some patients with acute gout (higher doses may cause side effects).
6) Intra-articular aspiration and injection of long-acting steroid is safe and effective for acute gout attacks.
7) Urate-lowering therapy is necessary for patients with recurrent acute attacks, arthropathy, tophi, or radiological changes of gout.
8) Therapeutic goal of urate-lowering therapy is maintenance of the SUA level below 6.8 mg/dL for crystal dissolution.
9) Allopurinol is appropriate as a long-term urate-lowering drug (100 mg daily and increased every two to four weeks) as required to achieve a specific serum urate acid goal. Doses must be balanced to the patient's renal status, uric acid level, and toxicity.
10) Uricosuric agent (e.g., probenecid) is an alternative to allopurinol in those with normal renal function (contra-indicated in urolithiasis).
11) Prophylaxis against acute attacks during the first months of urate-lowering therapy includes colchicine and/or NSAIDs.
12) Gout associated with diuretic therapy: consider stopping diuretic therapy; if possible use losartan and fenofibrate with comorbidities of hypertension/hyperlipidemia.

EULAR: European League Against Rheumatism; NSAIDs: non-steroidal anti-inflammatory drugs; SUA: serum uric acid. Source: Reference 27.

healthcare clinicians about the potential drug interactions and side-effects of urate-lowering agents. Finally, treatment of asymptomatic hyperuricemia is not recommended.[7]

Allopurinol

One traditional approach to the treatment of gout since 1965 is the prescription of allopurinol, an isomer of hypoxanthine. Allopurinol is a substrate for xanthine oxidase. The product binds with such high affininity that the enzyme cannot be oxidized in its normal substrate. Uric acid production is diminished, and xanthine and hypoxanthine levels in the blood rise. Xanthine and hypoxanthine are more soluble than urate and are less likely to deposit as crystals in the joints. The allopurinol dose must be adjusted in patients with renal impairment.[6]

Administration of allopurinol is often started at 100 mg per day, and the daily dosage is increased in 100 mg increments every two to four weeks.[8,9,26,27] The usual dosage range for allopurinol is 200-300mg/day for mild gout and 400-600mg/day for cases of moderate and severe gout. Up to five percent of patients are unable to tolerate allopurinol due to adverse effects such as rash, nausea, and bone marrow suppression.[32] If a serve rash occurs, the podiatrist should advise discontinuation of allopurinol. Allopurinol has fewer drug interactions than uricosuric agents.[6] Despite allopurinol's limitations, it is extensively used for most gouty patients and is considered safe and effective.[28]

Certain drugs used to treat gout, particularly thiazide diuretics and the use of cyclosporine in transplant patients, have been implicated in gouty attacks.

Emerging Therapies

Uricosuric agents, which enhance the renal clearance of urate (and were first used at the end of the 19th century[5]) are considered to be a second-line therapy for patients who are intolerant to allopurinol. Of all the older urate-lowering drugs, probenecid or sulfinpyrazone may be prescribed in patients refractory to allopurinol therapy.[29]

In the U.S., probenecid is the only potent uricosuric agent available.[8,9] Probenecid is most useful in patients with mild gout and normal renal function. Its mechanism of action is through the inhibition of the URAT1 transporter involved in the re-absorption of uric acid.[8,9]

Uricosuric therapy is contraindicated in patients with a history of nephrolithiasis and is not effective in patients with a creatinine clearance of less than 50 mL/min. Finally, both losartan and fenofibrate have slight uricosuric properties and may be useful as adjunctive therapy in gout patients with co-morbidities of hypertension and hyperlipemia.[6,8,27,33]

Febuxostat

Febuxostat is a potent, new selective xanthine oxidase inhibitor that received FDA approval in February 2009 for the management of hyperuricemia in patients with gout. It goes under the trade name of Uloric® and is distributed by Takeda Pharmaceuticals America.[8,9,34,35] This agent is not a purine analog and has a mechanism similar to that of allopurinol.[35] The recommended starting dose of febuxostat (Uloric®) is 40 mg per day.[8,35]

For patients who do not achieve a serum uric acid less than 6 mg/dL after two weeks at 40 mg, increasing the dose to 80 mg is recommended.[35] Febuxostat has demonstrated efficacy superior to that of allopurinol.[28,35] It is primarily metabolized by the liver and may be an alternative agent for patients with renal insufficiency. The adverse effect profile for febuxostat includes elevation in liver enzymes, rash, diarrhea, and headache.[8,9,35]

Takeda Pharmaceuticals America reported that febuxostat has a higher cardiovascular thromboembolic event rate than allopurinol.[35] Finally, Uloric® is contraindicated for patients treated with azathioprine, mercaptopurine, or theophylline.[35]

Uric Acid Oxidase

Uric acid oxidase, also

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TABLE 3
Medications Altering Urate Levels

Urate-Increasing Agents	Urate-Decreasing Agents
Beta-blockers	*Uricosurics*
Cyclosporine	Amlodipine
Diuretics	Fenofibrate
Ethambutol	Losartan
Lactate, B-hydroxybutyrate, acetoacetate	Probenecid
Nicotinate	Salicylates (high dose)
Pyrazinamide	*Xanthine Oxidase Inhibitors*
Salicylates (low dose)	Allopurinol
Tacrolimus	Febuxostat

Adapted from Choi HK, et al. Ann Intern Med. 2005; 143: 499-516

known as uricase, is an enzyme that catalyzes the conversion of uric acid to allantoin, which is present in all mammals except humans and higher primates.[28] There is interest in using uricase therapies to lower serum uric acid.

Rasburicase, a recombinant uricase IV product indicated for tumor lysis syndrome, might be successfully used in unusually severe cases of gout.[36] Rasburicase has a black box warning for anaphylaxis, hemolysis, and methemoglobin. Pegloticase (pegylated recombinant porcine uricase) has also demonstrated urate-lowering efficacy.[15,37]

The addition of polyethylene glycol (PEG) prolongs the half-life of uricase and decreases its antigenicity. Intravenous administration of PEG-uricase has been investigated for the potential treatment of severe tophaceous gout in patients hypersensitive to allopurinol.[38]

Finally, podiatric physicians should understand the contra-indications to both NSAIDs and corticosteroids symptomatic to existing therapies. Therefore, attention has been directed to recent advances in the understanding of gouty inflammation and the pro-inflammatory role of several cytokines in the pathophysiology of acute gout.[26,39]

Early, small-scale clinical trials have identified interleukin-1B as the most prominent cytokine in acute gout and indicate that the practice of inhibiting interleukin-1B may be efficient and safe in terminating the symptoms of acute gouty arthritis.[26]

Conclusion

Gout is a monosodium urate monohydrate crystal deposit disease. It was among the earliest diseases to be recognized as a clinical entity. Clinical podiatric physicians need to be equipped with pertinent knowledge to assist other clinicians in achieving successful patient outcomes when treating gout. To this end, new insights into the pathogenesis of hyperuricemia and gout have been reviewed.

Risk factors, typical presentations of symptoms, and key diagnostic parameters have been presented to inform podiatrists and help provide better patient care. Both non-pharmacologic modalities and pharmacologic therapies have been discussed, with the aim

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TABLE 4
Pharmacotherapy for Acute Gout Attacks

Drugs	Cautions	Comments
NSAIDs		
Indomethacin 50 mg tid (4-10 days) Naproxen 500 mg bid (4-10 days) Sulindac 200 mg bid (4-10 days)	Elderly patients, renal insufficiency, heart failure, peptic ulcer, liver disease, and concurrent anticoagulants (interactions with warfarin)	All NSAIDs are effective
Corticosteroids		
Prednisone 20-40 mg daily (2-3 days; taper over 10-14 days) Intra-articular methylprednisone 20-40 mg dose Intra-muscular methylprednisone 80-120 mg dose	Avoid in patients with septic joints; use with caution in patients with diabetes	Intra-articular therapy is treatment of choice if 1 or 2 accessible joints are involved
Colchicine		
0.6 mg orally bid or tid 0.6 mg orally daily or q48h (depending on renal clearance)	Avoid in severe renal or hepatic impairment because it can lead to bone marrow suppression and neuromyopathy; interacts with macrolides and statins	Use within first 24 hours of the attack; reduce dosage in older patients; diarrhea limits its use; avoid IV preparation

Adapted from Dore RK. Gout: what primary care physicians want to know. J Clin Rheumatol 2008; 14 (suppl5) S47-S54

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of increasing adherence through improved medication counseling. ■

References

[1] Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. Arthritis Rheum. 2008;58:15-25.

[2] Lawrence RC, Felson DT, Helmick CG, et al. Estimates of prevalence arthritis and other rheumatic conditions in the United States. Part II. Arthritis Rheum. 2008; 58:26-35.

[3] Weaver AL. Epidemiology of gout. Cleve Clin J Med. 2008;75(suppl 5):S9-S12.

[4] Pillinger MH, Rosenthal P, Abeles AM. Hyperuricemia and gout. Bull NYU Hosp Jt Dis. 2007;65:215-221.

[5] Nuki G, Simkin PA. A concise history of gout and hyperuricemia and their treatment. Arthritis Res Ther. 2006;8(suppl 1):S1.

[6] Dore RK. Gout: what primary care physicians want to know. J Clin Rheumatol. 2008;14(suppl 5):S47-S54.

[7] Weaver AL, Cheh MA, Kennison RH. How PCP education can impact gout management: the gout essentials. J Clin Rheumatol. 2008;14(suppl):S42-S46.

[8] Smith RG The diagnosis and treatment of gout. US pharmacist 2009 34 (5) 40-47.

[9] Mandel DA, Simkin PA. Gout: update on pathogenesis, diagnosis, and treatment. New Develop Rheum Dis. 2007;20-25. www.medpub.com/NDRDv4n3_Simkin.pdf . Accessed February 26, 2009.

[10] Choi HK, Mount DB, Reginato AM. Pathogenesis of gout. Ann Intern Med. 2005;143:499-516.

[11] Wyngaarden JB. The role of the kidney in pathogenesis and treatment of gout. Arthritis Rheum. 1958;1:191-203.

[12] Choi HK, Atkinson K, Karlson EW, et al. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow up study. Arch Intern Med. 2005;165:742-748.

[13] Choi HK, Atkinson K, Karlson EW, et al. Alcohol intake and risk of incident gout in men: a prospective study. Lancet. 2004;363:1277-1281.

[14] Choi HK, Atkinson K, Karlson EW, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med. 2004;350:1093-1103.

[15] Pillinger MH, Keenan RT. Update on the management of hyperuricemia and gout. Bull NYU Hosp Jt Dis. 2008;66:231-239.

[16] Emmerson BT. Effect of oral fructose on urate production. Ann Rheum Dis. 1974;33:276-280.

[17] Choi JW, Ford ES, Gao X, Choi HK. Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey. Arthritis Rheum. 2008;59:109-116.

[18] Schlesinger N, Schumacher HR. Update on gout. Arthrithis Rheum. 2002;47:563-565.

[19] Roubenoff R. Gout and hyperuricemia. Rheum Dis Clin North Am. 1990;16:539-550.

[20] Wallace KL, Riedel AA, Joseph-Ridge N, Wortmann R. Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care populations. J Rheum. 2004;31:1582-1587.

[21] Hawkins DW, Rahn DW. Gout and hyperuricemia. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. Pharmacotherapy: A Pathophysiologic Approach. 5th ed. New York: McGraw-Hill; 2002:1659-1664.

[22] Becker MA, Jolly M. Clinical gout and the pathogenesis of hyperuricemia. In: Koopman WJ, Moreland LW, eds. Arthritis and Allied Conditions. 15th ed. Philadelphia, PA: Lippincott, Williams & Wilkins; 2005:2303-2339.

[23] Worthmann PL, Kelly WN. Gout and hyperuricemia. In: Harris ED Jr, Budd RC, Genovese MC, et al, eds. Kelly's Textbook of Rheumatology. 7th ed. Philadelphia, PA: WB Saunders Company; 2005:1402-1429.

[24] Mandell BF. Clinical manifestations of hyperuricemia and gout. Clev Clin J Med. 2008;75(suppl 5):S5-S8.

[25] Dalbeth N, McQueen FM. Use of imaging to evaluate gout and other crystal deposition disorders. Curr Opin Rheumatol 2009; 21 (2): 124-131.

[26] Becker MA, Chohan S. We can make gout management more successful now. Curr Opin Rheumatol. 2008;20:167-172.

[27] Zhang W, Doherty M, Bardin T, et al. EULAR evidence bases 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;65:1312-1324.

[28] Pascual E, Sivera F. Therapeutic advances in gout. Curr Opin Rheumatol. 2007;19:122-127.

[29] Li-Yu J, Clayburne G, Sieck M, et al. Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout? J Rheumatol. 2001;28:577-580.

[30] van Heyningen C, Watson ID. Troponin for prediction of cardiovascular collapse in acute colchicine overdose. Emerg Med J. 2005;22:599-600.

[31] Schumacher HR Jr, Chen LX. The practical management of gout. Cleve Clin J Med. 2008;75(suppl 5):S22-S25.

[32] Schlesinger N. Management of acute and chronic gouty arthritis: present state-of-the-art. Drugs. 2004;64:2399-2416.

[33] Eggebeen AT. Gout: an update. Am Fam Physician. 2007;76:801-808.

[34] Becker MA, Schumacher HR, Wortmann RL, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med. 2005;353:2450-2461.

[35] Uloric® Febuxostat Complete prescribing information http://www.uloric.com accessed April 13, 2009.

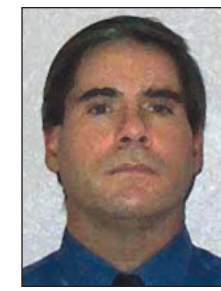
[36] Vogt B. Urate oxidase (rasburicase) for treatment of severe tophaceous gout. Nephrol Dial Transplant. 2005;20:431-433.

[37] Biggers K, Scheinfeld N. Pegloticase, a polyethylene glycol conjugate of uricase for the potential intravenous treatment of gout. Curr Opin Investig Drugs 2008; 9(4): 422-42.

[38] Terkeltaub R, Bushinsky DA, Becker MA. Recent developments in our understanding of the renal basis of hyperuricemia and the development of novel antihyperuricemic therapeutics. Arthritis Research & Therapy 2006; 8 (Suppl 1).

[39] Martinon F, Petrilli V, Mayor A, et al. Gout-associated uric acid crystals activate the NALP3 inflammasome. Nature. 2006;440:237-241.

Low doses of colchicine may be sufficient for some patients with acute gout.



Dr. Smith completed his postgraduate training with the College of Medicine at the University of Wales, Cardiff, Wales, UK in wound care and tissue repair. He is an associate of the American Professional Wound Care Association and a consultant to National Board of Podiatric Medical Examiners. He is a contributing editor and reviewer to JAPMA in the area of podiatric clinical pharmacology and has authored 50 refereed journal articles in the disciplines of pharmacy, podiatry, and wound care. He currently practices in Ormond Beach, FL.

EXAMINATION

Continuing Medical Education

See answer sheet on page 191.

1) Uric acid, the most insoluble of the purine substances, is a _____ containing three oxygen groups.
- A) Trinitropurine
- B) Trihydroxypurine
- C) Trioxypurine
- D) Trichloroxypurine

2) Non-modifiable risk factors for the development of gout include all of the following except:
- A) male or a postmenopausal female
- B) diet and medications
- C) genetic influences
- D) end-stage renal disease

3) At serum urate concentrations greater than _____, urate crystals may start to deposit.
- A) 3.4 mg/dL
- B) 4.5 mg/dL
- C) 2.8 mg/dL
- D) 6.8 mg/dL

4) When urate crystal deposits continue to accumulate, patients develop chronically stiff and swollen joints leading to the final stage known as_____.
- A) acute gouty arthritis
- B) asymptomatic hyperuricemia
- C) advanced gout
- D) intercritical period

5) Polarizing microscopic examination of synovial fluid reveals _____, confirming the diagnosis of gout.
- A) negatively birefringent crystals
- B) positively birefringent crystals
- C) negatively charged crystal particles and antibodies
- D) positively charged rhombi crystal particles

6) Dalbeth's and McQueen's review suggests _____ may improve non-invasive diagnosis of the crystal-induced arthropathies.
- A) Intra-operative observations
- B) interventional laboratory test
- C) microscopic examination of tophi
- D) high-resolution ultrasonography

7) Adjunctive therapy for gout and associated co-morbidities include that the patient do all of the following except_____.
- A) limit consumption of red meat
- B) replace consumption of fish with omega-3 fatty acids
- C) consume foods and drinks containing high fructose
- D) supplement diet with vitamin C

8) Low doses of _____ may be sufficient for some patients with acute gout.
- A) ibuprofen
- B) aspirin
- C) colchicine
- D) injectable corticosteroids

9) Since 1965, one traditional approach to the treatment of gout has been the use of the drug _____.
- A) indomethacin
- B) allopurinol
- C) prednisone
- D) sulindac

10) According to EULAR recommendations, _____ may be used as an alternative to traditional urate-lowering agents with normal renal function but are contraindicated in urolithiasis.
- A) Antibiotic agents
- B) non-pharmacologic agents
- C) intraarticular steroid agents
- D) uricosuric agents

11) According to this review, gouty attacks are usually associated with a _____.
- A) precipitating event
- B) hyperthermal event
- C) syncopal event
- D) infectious event

12) Identify which therapeutic agent may elevate serum uric acid.
- A) Fenofibrate
- B) Losartan
- C) Cyclosporine
- D) Amlopine

13) According to this review, the potential effect of co-administration of allopurinol and an angiotensin-converting enzyme inhibitor may _____.
- A) increase risk of rash
- B) increase the risk of allopurinol hypersensitivity
- C) increase risk of hypoglycemic effect
- D) increase risk for bleeding

14) The enzyme that catalyzes the conversion of uric acid to allantoin, and is present in all mammals except humans and higher primates, is known as_____.
- A) allantace
- B) hydroxuricase
- C) uric acid oxidase (uricase)
- D) oxyuricase

Continued on page 190

Continuing Medical Education

EXAMINATION

(cont'd)

15) Select a main component for the treatment of gout.
- A) Therapy of the acute attack
- B) Prophylaxis against gout flares
- C) Management of hyperuricemia
- D) All the above are main components

16) According to this review, several studies have demonstrated a link between_____.
- A) hyperuricemia and hypotension
- B) hyperuricemia and hypertension
- C) hyperuricemia and hyperkalemia
- D) hyperuricemia and hyperglycemia

17) The usual dosage range for allopurinol in cases of moderate and severe gout is_____.
- A) 50 mg—75 mg/day
- B) 200 mg—300 mg/day
- C) 400 mg—600 mg/day
- D) 40 mg—80 mg/day

18) The FDA-recommended starting dose for febuxostat the new selective xanathine oxidase inhibitor, is _____.
- A) 40 mg once a day
- B) 10 mg once a day
- C) 30 mg once a day
- D) 25 mg once a day

19) Corticosteroids are proven therapeutic agents for acute gouty attacks but must be avoided in patients with _____.
- A) hypokalemia
- B) hypoglycemia
- C) septic joints
- D) arthritis

20) Urate-lowering therapy is necessary for gout patients with_____.
- A) recurrent acute attacks
- B) arthropathy
- C) tophi and radiological changes
- D) all the above pathologies

See answer sheet on page 192.

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EXAM #8/09
Evolving Concepts in Gout Diagnosis and Treatment
(R. Smith)

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1.	A	B	C	D	11.	A	B	C	D
2.	A	B	C	D	12.	A	B	C	D
3.	A	B	C	D	13.	A	B	C	D
4.	A	B	C	D	14.	A	B	C	D
5.	A	B	C	D	15.	A	B	C	D
6.	A	B	C	D	16.	A	B	C	D
7.	A	B	C	D	17.	A	B	C	D
8.	A	B	C	D	18.	A	B	C	D
9.	A	B	C	D	19.	A	B	C	D
10.	A	B	C	D	20.	A	B	C	D

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