Supplement to *Clinical Geriatrics*

Management of Gout in the Elderly

New Solutions to an Age-old Disease

N. Lawrence Edwards, MD, FACP, FACR
Professor of Medicine
University of Florida
Gainesville, FL

Naomi Schlesinger, MD
Associate Professor of Medicine
Chief, Division of Rheumatology
UMDNJ/Robert Wood Johnson University Medical School
New Brunswick, NJ

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CONTINUING EDUCATION

TARGET AUDIENCE: The program is intended for geriatricians and other healthcare providers interested in optimizing the care of their older patients with hyperuriemia, and the signs and symptoms of gout.

LEARNING OBJECTIVES: At the conclusion of this activity, participants should be able to:

- Summarize the prevalence of gout in older patients and factors which may contribute to both primary and secondary hyperuricemia in this age group
- List the criteria for the staging of gout
- Enumerate the risk factors and co-morbidities that can contribute to, and exacerbate, flares of gout in older patients
- Optimize diagnostic testing to ensure maximal yield from these tests
- Consider the latest therapeutic options available for long standing gout and which are suitable for use in patients with renal and hepatic insufficiency.

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Fenofibrate - urate-lowering effect
Losartan - urate-lowering effect
IL-1 antagonists - acute gout flares
ACTH - acute gout flares
Pegloticase - treatment-failure gout

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California Assembly Bill 1195 requires continuing medical education activities with patient care components to include curriculum in the subjects of cultural and linguistic competency. It is the intent of the bill, which went into effect on July 1, 2006, to encourage physicians and surgeons, CME providers in the state of California, and the Accreditation Council for Continuing Medical Education to meet the cultural and linguistic concerns of a diverse patient population through appropriate professional development. The planners, speakers and authors of this CME activity have been encouraged to address issues relevant in their topic area. Additional resources and information about AB1195 can be found on our website at http://www.cme.uci.edu.

DISCLOSURE STATEMENTS

This activity has been peer reviewed for evidence base and fair balance.

AUTHORS

Dr Edwards serves as a consultant for Savient Pharmaceuticals, Inc., and Takeda Pharmaceuticals North American, Inc.

Dr Schlesinger, serves on the advisory board/speakers' bureau for Novartis, Savient Pharmaceuticals, Inc., and Takeda Pharmaceuticals North America, Inc.

STAFF

The following planning staff have nothing to disclose:

Alka Amin, Senior Associate Project Director, Strategic Consultants International, Hemel Hempstead, Herts, England

Kate Ackrill, Medical Writer, Strategic Consultants International, Hemel Hempstead, Herts, England

Bonnie Carroll, Director of CME, UCI School of Medicine, Irvine, California

Rebecca Yamarik, M.D. Peer Reviewer, UCI School of Medicine, Irvine, California

Robert W. Bennett, Director of CE, Purdue University School of Pharmacy and Pharmaceutical Sciences, West Lafayette, Indiana

Dawn Sinclair, CE Secretary, Purdue University School of Pharmacy and Pharmaceutical Sciences, West Lafayette, Indiana

HMP COMMUNICATIONS, LLC
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NEW SOLUTIONS TO AN AGE-OLD DISEASE

A continuing education supplement for healthcare professionals

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Faculty

N. Lawrence Edwards, MD, FACP, FACR
Professor of Medicine
Vice Chairman, Department of Medicine
University of Florida
1600 SW Archer Road, Room 4102
Gainesville
FL 32610-0277
Telephone: 352 265 0239
Fax: 352 338 9879
Email: Larry.Edwards@medicine.ufl.edu

Naomi Schlesinger, MD
Associate Professor of Medicine
Chief, Division of Rheumatology
Department of Medicine
UMDNJ/Robert Wood Johnson University Medical School
MEB 468
New Brunswick, NJ 08901
Telephone: 732-235-8378
Fax: 732-235-7238
Email: schlesna@umdnj.edu

Introduction

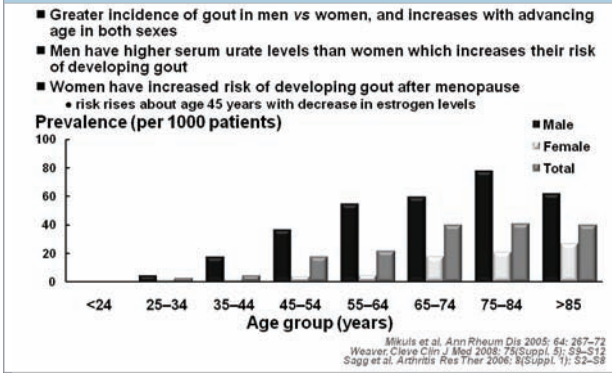
GOUT: SCALE OF THE DISEASE

N. Lawrence Edwards, MD and Naomi Schlesinger, MD

Gout is an inflammatory arthritis of metabolic origin which is triggered by crystallization of uric acid within joints. Gout is a growing concern, with both incidence and prevalence increasing worldwide; moreover, the clinical profile of gout appears to be growing more complex.[1,2] The prevalence of gout more than doubled in the USA between 1969 and 1985, with a current estimate of 5.1 million adults affected by gout in this country.[3] Prevalence of gout increases with advancing age in men, peaking at 75–84 years of age.[4] (**Figure 1**) In women, gout is essentially a disease of the elderly. Risk of gout in women is increased after the menopause, beginning to rise at around 45 years of age[5] Indeed, gout is the most common form of inflammatory arthritis in the elderly.[6] The prevalence of gout in a managed-care population increased from 21 per 1000 in 1990–92 to 41 per 1000 in 1999 in patients aged over 75 years and, over the same period, from 21–24 per 1000 to over 31 per 1000 in patients aged 65–74 years.[7]

Gout has a substantial impact on patients' lives. A study of US veterans found gout to be independently associated with higher medical and arthritic comorbidity, and higher primary care and inpatient utilization; patients with gout had poorer health-related quality of life (HRQoL), functional limitation, and higher mortality that were all attributable to higher comorbidity and sociodemographic characteristics.[8]

FIGURE 1: Age — a risk factor for gout.



CLINICAL MANIFESTATIONS OF GOUT IN SENIORS: CAUSES, CO-MORBIDITIES, AND COMPLICATIONS OF LONG-STANDING HYPERURICEMIA

N. Lawrence Edwards, MD

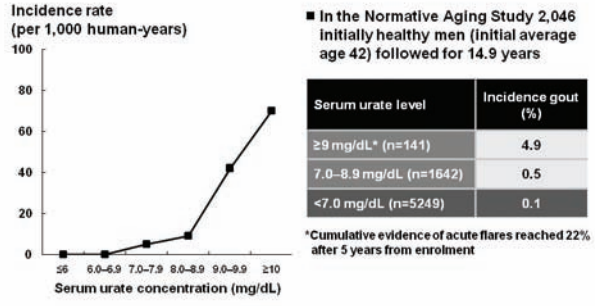
Staging of gout

Hyperuricemia is the condition in which serum urate (the end-product of purine metabolism) exceeds the limit of solubility in serum which is >6.8 mg/dL. Hyperuricemia, which results predominantly from inefficient renal excretion of uric acid (only a minority of cases are associated with increased uric acid synthesis), increases the risk of crystal deposition because of urate supersaturation. There is a direct positive association between hyperuricemia and future risk of developing gout, although not all individuals with hyperuricemia go on to develop gout.[9] (**Figure 2**) Gout is typically a progressive disease, with a period of asymptomatic hyperuricemia followed by an acute attack of gout involving urate crystallization, inflammation, and pain. (**Figure 3**) During the period between acute attacks, termed the intercritical phase, although the patient may be symptom free, tissue damage may be ongoing. If hyperuricemia remains uncontrolled, the condition may progress to the fourth stage, advanced gouty arthritis, involving formation of tophi (collections of urate crystals in soft tissue), polyarticular disease, urate nephrolithiasis, and interstitial nephropathy.

Risk factors for gout: Why gout is increasing (**Figure 4**)

A variety of risk factors and comorbidities are associated with gout; many of these are of particular relevance in the elderly and are increasing in incidence. Individuals with hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, cardiovascular disease, obesity, or the metabolic syndrome are all at increased risk of developing gout.[5] Because inefficient excretion of urate is the predominant cause of hyperuricemia, impaired renal function promotes hyperuricemia and is a risk factor for the development of gout;[1] chronic kidney disease affects nearly 20 million people in the USA, a number that is likely to grow as the population ages and the prevalence of diabetes mellitus and hypertension increase.[10] Furthermore, hyperuricemia may be an independent risk factor for chronic kidney disease.[11] Hypertension is an independent risk factor for gout. Up to 40% of patients with hypertension have gout and up to 50% of patients with gout have hypertension.[11,12] Obesity, which increases serum urate by increasing production and decreasing renal elimination, is also a risk factor for gout, with a

FIGURE 2: Serum urate as risk factor for gout.



Campion et al, Am J Med 1987; 82: 421–6
Saag et al, Arthritis Res Ther 2006; 8(Suppl.1): S2–S8

FIGURE 3: The four stages of gout.

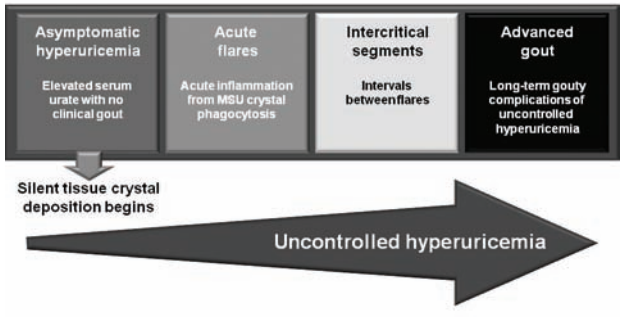


FIGURE 4: Selected risk factors and co-morbidities associated with gout.

Risk factor / co-morbidity	Evidence level	Adjusted RR	95% CI
Male	2b	7.64	7.46–7.81
Chronic renal failure	2b	4.95	4.28–5.72
Hypertension	2a	3.93	1.60–9.70
Obesity	2b	3.81	1.22–11.84
CHD	2b	1.75	1.70–1.79
Diuretics	2a	1.72	1.67–1.76
Seafood	2a	1.51	1.17–1.95
Meat	2a	1.41	1.07–1.86
Alcohol (beer/liquor)	2a	1.17	1.11–1.22
Diabetes	2b	1.11	1.06–1.16
TG	2b	Significant increase	

2a = Cohort studies; 2b = Case-control studies

- These factors should be considered and treated in their own right when treating a patient who presents with gout

BMI of 35 or more in men being associated with relative risk of gout of 2.97 (adjusted for a variety of factors including age, relevant medical history, and dietary intake) when compared the risk in men with a BMI of 21–22.9.[2,12] Around 60% of Americans are overweight, and obesity is forecast to be a growing problem in the aging US population and worldwide.[2,13,14]

Metabolic syndrome, comprises of a cluster of cardiometabolic conditions related to insulin resistance that is the forerunner of diabetes mellitus. Metabolic syndrome is a risk factor for cardiovascular disease and is found in 76% of gout patients in the USA;[15] in the general US population, metabolic syndrome is three times more common in patients with gout than in those without gout.[16] Insulin resistance is thought to promote renal urate reabsorption, and serum urate is around 0.5–1.0 mg/dL higher in patients with metabolic syndrome than in controls.[17,18] The prevalence of metabolic syndrome is increasing to epidemic proportions in the USA and it is also increasing in developing nations.[19,20] Furthermore, the prevalence of metabolic syndrome, and its prevalence in patients with gout, increase with age.[16,19]

Certain medications are associated with increased risk of gout. The use of diuretics is a significant risk factor in the development of gout as they increase renal reabsorption of uric acid. Thiazide diuretics are recommended as first-line therapy in most patients with hypertension, which may lead to increased incidence of gout secondary to diuretic use.[2,21] Low-dose aspirin, commonly prescribed for cardioprotection, promotes uric acid retention. In elderly patients (aged 61–94 years), a dose of aspirin 75 mg/day decreases urate excretion by 15% and causes a significant increase in serum urate.[22] Widespread use of low-dose aspirin may therefore contribute to increasing prevalence of gout. Cyclosporine, which increases tubular reabsorption of urate, can lead to a type of rapidly ascending gout that is often polyarticular; this problem has emerged along with increasingly successful organ transplant programs.[1,5,23]

Alterations in dietary and lifestyle choices are also likely to have contributed to increased rates of hyperuricemia and gout.[5] A diet rich in meat, particularly red meat, and seafood, such as shellfish, tuna, shrimp and dark fish, is associated with increased risk of development of gout, as is high intake of alcohol, particularly beer.[24,25] Although high intake of purines via these sources increases risk of gout, purine-rich vegetables, such as spinach, asparagus, cauliflower, mushrooms, peas, previously eliminated in low-purine diets, are not associated with hyperuricemia or increased risk of gout. In addition, relatively high consumption of dairy (low fat) products is associated with reduced risk of hyperuricemia and gout, possibly because of a uricosuric effect of dairy-derived proteins.[24,26] Increased consumption of fructose in sweetened foods and soft drinks over recent years is another factor that may have contributed to rising rates of gout.[26,27]

The rising prevalences of obesity, the metabolic syndrome, chronic kidney disease and end-stage renal failure, and hypertension, along with lifestyle factors such as increased alcohol consumption, are all likely to have contributed to the increase in gout prevalence.[1] The aging population will also contribute to increased longevity, with better survival in coronary artery disease, chronic heart failure; and diabetes mellitus contributes to higher gout prevalence as gout is an age-related condition, with elderly patients with longstanding hyperuricemia being at increased risk of developing symptoms. Gout secondary to diuretic therapy for hypertension and cardiac failure in the elderly is also a factor.

Pathophysiology of hyperuricemia and advanced gouty arthritis

In an acute attack of gout, monosodium urate (MSU) crystals initiate, amplify, and sustain an inflammatory attack involving cytokine release and phagocytosis of crystals.[28] An acute attack of gout usually lasts 7–10 days if untreated, but recurrence is common. Sixty percent of patients will experience another acute attack within 1 year, 78% within 2 years.[29] During the intercritical phase, uric acid deposits may continue to increase silently, and tissue stores of urate will continue to increase if hyperuricemia persists.[30] Persistent presence of crystals in the joint and chronic low level inflammation may lead to chronic synovitis, loss of cartilage, and bone erosion.[28] Over time, the frequency of acute attacks increases and polyarticular involvement becomes more common. Patients may eventually develop advanced gout, with chronically stiff and swollen joints and tophi. Tophi are formed by monosodium urate crystals surrounded by a granuloma-like tissue reaction.[31] It usually takes more than 10 years of recurring acute attacks of gout for tophi to develop, but around 30% of patients with gout who do not receive urate-lowering therapy for a 5-year period develop tophaceous gout, and 75% of untreated patients will develop severe tophaceous gout within 20 years of their initial attack.[32,33] More rapid development of tophi appears to be associated with advanced age, use of diuretics, the use of cyclosporine in transplant recipients, and with pre-existing osteoarthritis of the hands.[34–8] Tophi are commonly located on the joints of the hands or feet, but are also found on the ear, the olecranon bursa, and the Achilles tendon; tophi can occur over osteoarthritic nodes in the distal and proximal interphalangeal joints, especially in older women.[34] As tophi increase in size they engender a chronic mononuclear cell inflammatory response that destroys bone and cartilage. Chronic articular tophaceous gout can therefore cause persistent pain and nerve compression syndromes, and may lead to de-

structive arthropathy and chronic secondary osteoarthritis, resulting in loss of motion and function, deformity, bone erosions, and skin perforation.[29,34] Polyarticular advanced gouty arthritis with subcutaneous nodules can mimic rheumatoid arthritis.[34]

Clinical features of gout in the elderly

Clinically, gout in the elderly may differ from gout in the typical presentation in middle-aged males, with increased incidence in women, polyarticular onset with hand involvement (in contrast to the typically monoarticular onset in middle-aged men), earlier development and increased incidence of tophi, unusual localization of tophi on osteoarthritic nodes, and association with the use of diuretics.[39–41] The atypical presentation of gout in the elderly may hinder diagnosis and delay initiation of appropriate treatment.

FAQs

What factors are associated with metabolic syndrome in gout patients?

The metabolic syndrome has been defined in several different ways, but generally encompasses obesity (as indicated by waist circumference or waist-to-hip ratio), hyperlipidemia (raised triglycerides and low HDL cholesterol), hypertension, and raised fasting plasma glucose; the metabolic syndrome is a significant risk factor for cardiovascular disease, and predicts coronary and cerebrovascular disease.[18] Hyperuricemia and gout are frequently associated with the components of the metabolic syndrome. Serum urate concentrations increase with the number of components of the metabolic syndrome, even after adjustment for confounding factors such as age and diuretic use. Similarly, prevalence of the metabolic syndrome increases with increasing serum urate concentrations.[18] Most studies have shown that all components of the metabolic syndrome are correlated with urate levels, though the strongest correlation seems to be with waist circumference.[18]

What are the overall goals in managing patients with comorbidities?

When a patient presents with symptomatic gouty arthritis, the focus is on addressing their pain and inflammation. Once this is under control, however, it is important to address the underlying hyperuricemia by lowering serum urate, to treat or prevent gouty arthritis, and to identify and treat comorbidities. Because of the association between gout and comorbidities such as obesity, hypertension, and hyperlipidemia, a diagnosis of gout should act as a signal for the need to address as many modifiable risk factors as possible and to treat comorbid conditions appropriately. Addressing these risk factors will also help to reduce serum urate; for example, weight loss of 8 kg has been associated with a decrease of 11% in urate levels.[42]

Have any studies shown a decrease in cardiovascular disease or stroke events in patients associated with reducing serum urate to <6.0 mg/dL?

The link between hyperuricemia and the cardiovascular risk factors that constitute the metabolic syndrome has been considered in the past to be a non-etiologic relationship. However, recent evidence suggests that hyperuricemia is an independent risk factor for cardiovascular disease and hypertension.[11] High serum urate may be directly toxic to microvasculature, and hyperuricemia often precedes the development of the metabolic syndrome.[43,44] Although asymptomatic hyperuricemia in individuals at relatively low risk of cardiovascular disease (e.g. those with uncomplicated obesity, hypertension, or dyslipidemia) is probably a result of diminished renal urate excretion and not a reason to recommend urate-lowering therapy, hyperuricemia in patients with obesity, hypertension, or diabetes mellitus at high cardiovascular risk, such as those with overt ischemic events, may be a marker or even a promoter of inflammation, ischemia, and oxidative stress in the cardiovascular system.[18] Ongoing clinical trials will determine whether reducing serum urate reduces rates of cardiovascular disease and stroke.

MANAGEMENT OF GOUT IN SENIORS:
ADDRESSING BARRIERS AND SETTING GOALS FOR OPTIMAL CONTROL

Naomi Schlesinger, MD

Criteria for diagnosing gout

Acute gout typically has abrupt onset (2–4 hours) of severe joint inflammation, often at night, with warmth, swelling, erythema, and pain, sometimes with systemic symptoms (fatigue, fever, chills); the majority of first attacks (in men) are monoarticular. A definitive diagnosis of gout requires identification of monosodium urate crystals from a joint aspiration carried out during an acute attack. In practice, however, it is more common for a presumptive diagnosis to be made on the basis of clinical features. Criteria for diagnosing gout have been published by the American College of Rheumatology (ACR) (**Table 1**) and European League Against Rheumatism (EULAR).[45,46] The criteria of these two bodies are similar: Rapidly developing severe pain, swelling, and tenderness, especially with overlying erythema, is strongly suggestive of crystal inflammation (though not specific for gout). If this typical presentation reoccurs in the toe and there is hyperuricemia, a clinical diagnosis will be reasonably accurate.[47,48] Patients should be assessed for hyperuricemia, though it is important to be aware that serum urate may rise or fall during an acute attack, and may be normal during the painful period. Measuring serum urate 2 weeks after an acute attack is optimal. The absence of hyperuricemia between acute attacks makes a gout diagnosis unlikely.[48] X-ray may reveal typical 'punched-out' periarticular erosions with overhanging edges, but these changes are not seen radiographically until 6–12 years after the initial acute attack. Ultrasonography can detect deposition of monosodium urate crystals on cartilaginous surfaces, tophaceous material, and typical erosions.[49] Patients with gouty arthritis find that topical ice helps relieve joint pain, in contrast to patients with rheumatoid arthritis or other inflammatory arthritic conditions. Application of topical ice should be part of the history taken and physical examination in cases of suspected acute gout or where the nature of an inflammatory arthritis is unclear.[50]

TABLE 1: American College of Rheumatology preliminary criteria for the classification of acute arthritis of primary gout[45]

Gout may be diagnosed if either of these criteria are present	Monosodium urate crystals in synovial fluid during the attack
	Tophi confirmed with crystal examination
Gout may be diagnosed if at least six of these criteria are present	More than one attack of acute arthritis
	Maximum inflammation developing within a day
	Monoarthritis
	Redness over joints
	First metatarsophalangeal painful/swollen
	Unilateral first metatarsophalangeal attack
	Unilateral tarsal joint attack
	Suspected tophi
	Hyperuricemia
	Asymmetric swelling within a joint on X-ray
	Synovial fluid culture negative for organism during the attack
	Subcortical cysts without erosions on X-ray

Treatment goals: Challenges in the elderly

The goals of treatment of gout depend on the stage of gout that is being addressed. At all stages, however, management of gout in the elderly presents challenges. Physiological changes associated with aging mean that the threshold for toxicity of therapeutic agents is lower in the elderly and side-effects may be more pronounced.[34,51] Age-associated decline in glomerular filtration rate (GFR) is of particular significance and may necessitate dosage reduction or restricting therapeutic options; although age-related decline in GFR is somewhat variable, only 2% of patients aged over 70 years are likely to have normal renal function and over 75% may have a moderate or severe decrease in GFR.[52] In addition to age-related physiological changes, there is a greater frequency of comorbid illnesses such as chronic kidney disease (often secondary to diabetes mellitus or hypertension), peptic ulcer disease, and congestive heart failure, coupled with multiple concomitant drug use, that may impose limitations on choice of medication or increase risk of drug interactions.[6,40] Socioeconomic factors and age-related cognitive decline may also affect compliance with lifestyle modifications, medications, and monitoring.

Acute gout: Goals and approaches

The goal of treatment of acute gout is to relieve pain and inflammation and terminate the attack as quickly as possible. Rest-

ing the affected joint and application of topical ice are helpful non-pharmacological approaches in acute gout.[53–5] Pharmacotherapy, however, is almost universally necessary for prompt resolution. Although patients will eventually show some spontaneous improvement, resolution of an acute attack within 7 days is unlikely without the use of therapy.[56] Issues critical to the treatment success are rapid initiation, adequate dosing, and appropriate duration of anti-inflammatory therapy; treatment should be continued until the flare has resolved and then tapered for several days until all signs of inflammation have disappeared.[57]

Pharmacotherapeutic options for acute gout are non-steroidal anti-inflammatory drugs (NSAIDs), oral colchicine, corticosteroids, or adrenocorticotrophic hormone (though this is rarely used today owing to excessive cost). Choice of anti-inflammatory medication will be influenced by the patient's comorbidities and concurrent medications; these factors are even more significant in the elderly. Several NSAIDs are available for acute gout, all of which appear to be equally effective when used at the full anti-inflammatory dose.[57] Corticosteroids are a valuable option in patients with poor renal function and can be given parenterally in those unable to take oral medication.[6] Oral and intravenous colchicine were 'grandfathered' before FDA drug toxicity laws came into force in 1969; colchicine has the smallest benefit-to-toxicity ratio of the drugs used for acute gout, and in the intravenous form, at least, is no longer recommended because of adverse reactions, including death.[6,58] Oral colchicine may be used as second-line therapy when NSAIDs or corticosteroids are contraindicated or ineffective; dose reduction in the elderly is appropriate and limited to 1.8 mg in the first 24 hours and 1.2 mg thereafter until symptoms resolve. This will greatly limit the common adverse effects of vomiting and diarrhoea that place the elderly at risk of dehydration.[6,59]

Chronic gout: Goals and approaches

Treatment of the acute attack does not, however, address the underlying cause of gout – hyperuricemia – or prevent disease progression. In chronic gout, the goals of treatment are to lower serum urate to ≤6.0 mg/dL, without drug toxicity, to mobilize and deplete crystals, and deplete the total body urate pool to a level at which acute flares will be prevented. It is also necessary to protect against further attacks while the urate pool is being lowered, to address lifestyle factors that may be contributing to disease, and to recognize and treat associated comorbidities.[57]

Dietary modifications, to reduce animal-derived purine intake and encourage weight loss (including moderation in intake of cholesterol and saturated fatty acids), reduction in alcohol intake, and introduction of regular exercise should be encouraged if appropriate, and may help other conditions associated with gout. Soft drinks sweetened with fructose also increase serum urate levels, such that their intake should be limited.[27] Increased consumption of dairy products may be recommended, particularly low fat diary products.[24] Modifications such as these may be sufficient in some patients with early mild gout, but in general they do not lower serum urate sufficiently to obviate the need for urate-lowering therapy in patients with existing gout.[57] In addition, only 20% of patients seeking medical care are ready to change unhealthy behaviors, and changes in lifestyle may be impractical and difficult to sustain.[6,39] Medications that may be contributing to hyperuricemia should be altered if possible: Thiazide diuretics taken for hypertension could be substituted by the angiotensin II receptor inhibitor, losartan, which has a mild uricosuric effect and may be particularly suitable for patients with gout and hypertension.[6] Patients taking thiazide diuretics for congestive heart failure may benefit from switching to a loop diuretic or a potassium-sparing diuretic.

Pharmacological management is recommended for patients with 2 or more attacks of gout per year, patients with tophi, joint damage, polyarticular or difficult-to-treat attacks, or persistent synovitis; treatment is also recommended for patients with uric acid overproduction (though not with a uricosuric drug).[60.61] To optimize compliance it is important that patients understand why they need to take urate-lowering therapy and how it should be taken. In particular, patients should be made aware that they will experience an increase in flares in the first few months of therapy and this subsides once the target serum urate level has been reached, in addition intermittent therapy or withdrawal of agents leads to recurrence of disease, so urate-lowering therapy should be life-long once initiated.[6] To be effective, urate-lowering therapy should be given at a dose sufficient to lower serum urate to <6.0 mg/dL, a concentration below the limit of solubility of urate crystals and at which crystals will be depleted. Continuous reduction of serum urate to <6.0 mg/dL has been demonstrated to reduce or eliminate acute flares,[62–4] to reduce urate crystal stores in the joints,[65] and to reduce tophus size.[64,66,67] Serum urate therefore needs to be monitored regularly to ensure that the target level of <6.0 mg/dL is achieved and maintained: Urate levels should be monitored every 4–6 weeks after initiation of urate-lowering therapy, with dosage adjustments if necessary, until the target level is reached, then every 6–12 months to make sure a level <6.0 mg/dL is maintained.

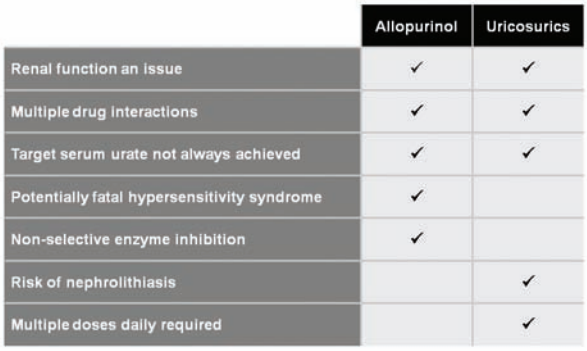
Sudden decrease in serum urate can precipitate a gout flare, such that the risk of acute gout flares is *increased* early in the course of urate-lowering treatment. Such treatment-initiated flares, also called "mobilization flares", have an impact on patient adherence to therapy. For this reason, therapy should not commence for at least 3 weeks after all symptoms of an acute attack of gout have resolved, and anti-inflammatory prophylaxis should be used when urate-lowering therapy is initiated. Colchicine or NSAIDs may be used in this setting, at doses lower than the full anti-inflammatory dose, provided there are no contraindications and the patient is monitored appropriately. The efficacy of colchicine in reducing flares during initiation of allopurinol has been demonstrated in a randomized, placebo-controlled prospective trial: Patients treated with colchicine experienced significantly fewer and less severe flares than patients given placebo.[68] Prophylactic ther-

TABLE 2: Urate lowering drugs

Category	*Mode of action*	*Examples*
Uricostatic drugs	Decrease uric acid synthesis (inhibit xanthine oxidase)	Allopurinol Febuxostat
Uricosuric drugs	Inhibit urate reabsorption in the proximal tubule	Probenecid Sulphinpyrazone Benzobromarone* Losartan Fenofibrate
Uricolytic drugs	Degrade uric acid	Uricase

*Withdrawn from the market owing to concerns about hepatotoxicity.

FIGURE 5: Limitations to existing arsenal of urate-lowering agents.



apy should begin 2–3 weeks before urate-lowering medication is initiated, and be continued for at least 6 months, ideally until the target serum urate level has been reached and maintained and the patient has not experienced a gout flare for 6 months.[6]

Urate-lowering agents fall into three categories – uricostatic, uricosuric, and uricolytic drugs (**Table 2**). Allopurinol, a non-selective xanthine oxidase inhibitor, is currently the first-line urate-lowering agent, and can be used in both urate overproducers and urate underexcretors. In contrast to uricosuric agents increase urinary excretion of urate and are therefore not suitable for use in patients with gout resulting from overproduction of urate. A major limitation of both allopurinol and uricosuric agents is that serum urate targets are frequently not achieved.[57] Allopurinol is approved to be used in doses between 100 and 800 mg/day but is rarely used in doses above 300 mg/day. Doses of allopurinol at 300 mg/day or less results in urate lowering to the target of less than 6.0 mg/dL in only 40% or less of treated subjects. Renal function is an issue with both allopurinol and uricosuric agents; dosage adjustment has been recommended if allopurinol is used in patients with chronic kidney disease. Uricosurics, require an adequate level of renal function (creatinine clearance >50 mL) to be effective.[6,51]

Drug interactions are also a problem with both allopurinol and uricosurics. Allopurinol shows pharmacokinetic interactions with several drugs, some potentially hazardous (in particular, mercaptopurine and azathioprine).[69] NSAIDs interfere with the effect of uricosuric agents on the renal tubules; NSAIDs may be co-prescribed with probenecid, but close monitoring is required in the elderly.[70] Uricosurics increase risk of nephrolithiasis such that fluid intake needs to be increased.[57] Allopurinol causes rash in around 2% of patients;[43] around 20% of patients report side-effects and 5% discontinue the drug.[71] Allopurinol can also cause a rare but potentially fatal hypersensitivity syndrome that is associated with renal impairment and the use of diuretics, and its toxicity increases with age.[6,51] Allopurinol hypersensitivity syndrome involves fever, rash (toxic epidermal necrolysis, erythema multiforme or a diffuse macropapular or exfoliative dermatitis), eosinophilia, hepatic abnormalities, and acute renal failure. Allopurinol should be discontinued if a rash develops as this can be a precursor of severe systemic hypersensitivity.[57] The limitations of allopurinol and uricosuric agents are summarized in **Figure 5**.

Febuxostat is a novel agent that received FDA approval for 40 mg and 80 mg daily doses, for the chronic treatment of hyperuricemia in early 2009. Febuxostat is a specific inhibitor of xanthine oxidase that has been shown to be safe and effective in lowering serum urate, with a dose of 80 mg daily being more effective than allopurinol 300 mg daily.[72] Febuxostat is well tolerated in long-term treatment and in patients experiencing hypersensitivity or intolerance to allopurinol, and dose adjustment is not necessary in the elderly or in patients with stage 2 or 3 chronic kidney disease (creatinine clearance 30–89 mg/dL).[72] The febuxostat *versus* allopurinol trial (FACT), a 52-week trial in 762 patients with initial serum urate ≥8.0 mg/dL, showed that with febuxostat 80 mg (FDA approved dose) or 120 mg daily a significantly greater proportion of patients achieved target serum urate <6.0 mg/dL than with allopurinol 300 mg daily.[73] The CONFIRMS trial, a Phase 3, 6-month trial of 2269 patients with gout and serum urate >8.0 mg/dL, including those with moderate chronic kidney disease (n=145), were randomized to receive febuxostat 40 mg or 80 mg daily, or allopurinol 300 mg daily (dose adjusted to 200 mg in patients with chronic kidney disease). This trial showed that febuxostat 80 mg is more efficacious than febuxostat 40 mg dose and allopurinol 300 mg in lowering serum urate to <6.0 mg/dL. In addition, the trial demonstrated that febuxostat 40 mg and 80 mg is superior in lowering serum urate compared to allopurinol 200 mg in patients with gout and chronic kidney disease.[74] (**Figure 6**) FOCUS, a 5-year trial assessing the long-term safety and efficacy of febuxostat (initial dose 80 mg daily with adjustment to 40 mg or 120 mg daily as necessary during weeks 4–24) found that most patients achieved durable maintenance of serum urate <6.0 mg/dL, and that this sustained reduction in serum urate was associated with near complete elimination of gout flares.[75] (**Figure 7**) The most common adverse events reported with febuxostat were abnormal liver function tests, headache, and gastrointestinal symptoms. These were usually mild and transient, and there have been no reports of severe hypersensitivity like that asso-

FIGURE 6: Febuxostat *vs* allopurinol in lowering SU <6 mg/dL in patients with gout and Chronic Kidney Disease (CKD).

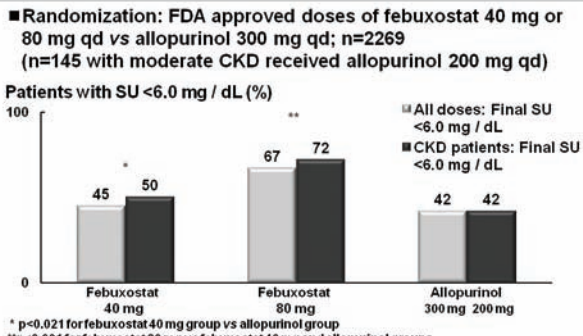
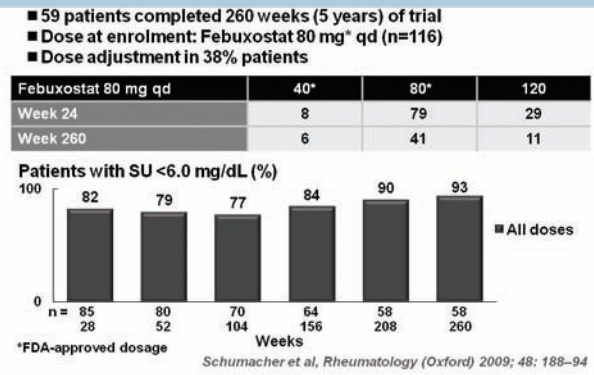


FIGURE 7: FOCUS study to assess long-term efficacy of lowering SU <6 mg/dL.



ciated with allopurinol. Febuxostat has a low potential for drug–drug interactions in clinical use; in particular, it does not interact with NSAIDs or warfarin, commonly prescribed in the elderly.[76,77] Like allopurinol, febuxostat may interact with drugs that are metabolized by xanthine oxidase (theophylline, mercaptopurine, azathioprine). Febuxostat may provide an alternative treatment choice for elderly patients, particularly those with chronic kidney disease.

Pegloticase is a pegylated recombinant mammalian urate oxidase which has been studied in patients for whom conventional therapy such as allopurinol is ineffective or contraindicated (treatment-failure gout). Pegloticase requires intravenous infusion at frequent intervals every 2 or 4 weeks. Early published results from phase 3 clinical trials examined the percentage of subjects with plasma urate levels below 6.0 mg/dL for >80% of the time in months 3 and 6 as the primary endpoint. In this hard to treat population 42% of the every 2 week infused subjects and 34% of the every 4 week infused subjects achieved target. A secondary endpoint was resorption of tophus burden. There was complete tophus resolution in 40% of subjects receiving every 2 week infusions.[78] Pegloticase remains under review by the FDA.

FAQs

How should asymptomatic hyperuricemia be managed?

Asymptomatic hyperuricemia should alert a physician to investigate a correctable cause such as alcohol abuse, medications, or an underlying metabolic condition or malignancy, and to address potential cardiovascular risk factors and comorbidities (such as obesity).[79] Dietary and lifestyle modifications or alterations in medication (such as a switch from a thiazide diuretic, or initiation of an agent for another indication that has uricosuric properties such as losartan or fenofibrate) may be appropriate, but, at present, pharmacological treatment of asymptomatic hyperuricemia in order to prevent development of gout is not generally recommended, because the risk:benefit ratio of pharmacologic lowering of uric acid has not been examined in this setting. Another reason for not treating asymptomatic hyperuricemia is that allopurinol hypersensitivity syndrome has in the past occurred most often as a consequence of treatment of asymptomatic hyperuricemia.[30,79-81] Exceptions include patients about to undergo chemotherapy or radiotherapy likely to cause extensive cell lysis, and patients with exceptionally high serum urate levels (≥12 mg/dL in men or ≥10 mg/dL in women).[79] However, the mounting evidence that uric acid may be an independent risk factor in the development of vascular diseases in addition to gout may change the way asymptomatic hyperuricemia is viewed and may alter future therapeutic interventions.[82]

What specifically are purine-rich foods?

High consumption of seafood and meat increases risk of developing gout, as does high consumption of alcohol, particularly beer.[24,25] Meat, seafood, and beer are all high in purines. Foods with the highest purine content include red meat, particularly organ meat (liver, kidney, brain, sweetbreads), veal, venison and turkey, shellfish, small fish such as sardines, anchovies, and herring, and some large fish (cod, haddock); these foods are best avoided by gout patients.[29,79] Foods with a moderate purine content, that may be eaten occasionally, include chicken, duck, ham, and pork.[29] Although some vegetables, such as asparagus, spinach, beans, lentils, and mushrooms, have a moderately high purine content, consumption of purine-rich vegetables is not associated with increased risk of gout and need not be restricted.[24]

Should patients have joint aspiration for crystal confirmation before starting treatment?

Crystal-proven diagnosis of gout is considered the gold standard to establish a definitive diagnosis of gout, but there are no studies comparing cost and clinical outcome of crystal-proven diagnosis *versus* clinical diagnosis,[83,84] and synovial fluid analysis is rarely performed in practice.[61,85] Primary-care practitioners may be reluctant to carry out and patients reluctant to undergo this procedure routinely in painful, inflamed joints. Inexperience, time pressures, and inaccessibility of polarizing microscopy are additional factors limiting the use of

synovial fluid analysis.[61] The practical approach is to carry out joint aspiration if there is reasonable doubt about the diagnosis, particularly for a suspected first presentation of acute monoarthritis where septic arthritis must be in the differential diagnosis.[45,46] A clinical diagnosis in the absence of synovial fluid analysis must however involve: a careful patient and family history, including questions about comorbid conditions commonly associated with gout and previous history of acute joint pain and swelling in the absence of trauma; identification of current medications that may be associated with hyperuricemia; and a thorough physical examination.[45-47]

Are NSAIDs appropriate for treatment of acute attacks in older patients?

Because of their more favorable adverse event profile, NSAID therapy is preferred over colchicine for an acute gout flare in patients without complications.[6,59] In the elderly, traditional colchicine regimens have been associated with adverse event rates of 50–80%.[6] Side effects of NSAIDs are, however, more pronounced in the elderly, and NSAIDs are relatively contraindicated in patients with chronic kidney disease or congestive heart failure and are best avoided in patients with peripheral edema, peptic ulcer disease, or gastrointestinal bleeding, or those taking warfarin.[6,57,86] In addition, indomethacin has been associated with behavioral changes in elderly patients.[87,88] Because of these concerns, caution is needed when prescribing NSAIDs for the treatment of acute gouty arthritis in the elderly; NSAIDs with a short half-life are preferred because of the more rapid reversal of any renal dysfunction or electrolyte abnormalities.[6,89] Gastroprotective agents (proton pump inhibitors) may reduce risk of gastrointestinal bleeding associated with NSAID use in the elderly.[6]

What dosage of allopurinol is used in clinical practice to achieve serum urate <6.0 mg/dL?

The use of insufficient dosages of allopurinol is one of the most common barriers to effective control of hyperuricemia in the elderly population. The vast majority of allopurinol prescriptions are for doses ≤300 mg/day, a level at which hyperuricemia will often be inadequately treated.[90] Data from clinical trials indicate that only 21%–55% of patients will attain a serum urate <6.0 mg/dL on a daily dose of allopurinol 300 mg.[6] This situation has arisen because of longstanding, non-evidence-based (but endorsed by the FDA) guidelines intended to avoid allopurinol hypersensitivity syndrome, particularly in patients with chronic kidney disease. However, allopurinol hypersensitivity syndrome may occur even at low doses of allopurinol.[91] Adherence to dosing guidelines according to creatinine clearance therefore does not prevent hypersensitivity reactions and yields suboptimal control of hyperuricemia.[92] Inadequate control of hyperuricemia also results in part from lack of adherence to published standards of care, particularly monitoring of serum urate: Over 80% of patients commencing allopurinol therapy do not have their serum urate levels measured within 6 months.[61]

Allopurinol is approved at doses of up to 800 mg/day; an average dose of 400–600 mg/day is required to normalize serum urate in patients with moderately severe tophaceous gout.[94] Allopurinol should be initiated at a low dose and increased gradually, according to current treatment guidelines, with close monitoring of serum urate.[91,95]

How should patients with gout and renal impairment be managed?

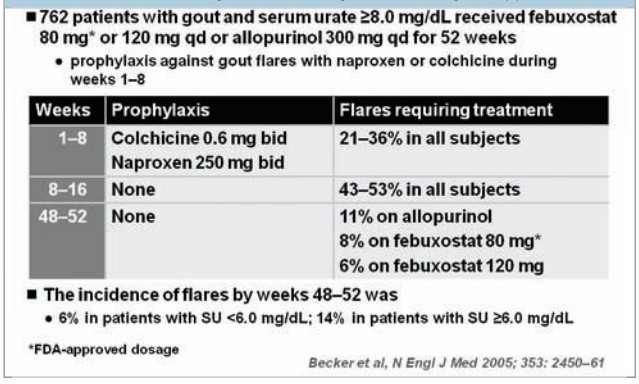
Renal impairment is common in patients with gout: A study of hospitalized patients with acute gout found 73% to have reduced GFR.[96] Probenecid requires sufficient renal function (GFR >50 mL/min) to be effective, and is therefore unsuitable for patients with stage 4 chronic kidney disease (GFR 15–29 mL/min) and many with stage 3 disease (GFR 30–59 mL/min).[6] The risk of allopurinol hypersensitivity syndrome is increased in patients with renal impairment, such that allopurinol should be initiated at a low dose in these patients;[57] however, dosages of allopurinol adjusted according to creatinine clearance do not provide adequate control of hyperuricemia.[91,92] In a patient with chronic kidney disease and severe and persistent hyperuricemia, allopurinol dose escalation above the guideline recommendations only be considered, with very careful monitoring of serum urate as well as markers of hypersensitivity such as transaminase elevation, leukocytosis, and eosinophilia.[91] The alternative strategy is to use febuxostat, for which no dose adjustment is necessary in patients with stage 2 or 3 chronic kidney disease. Clinical trials demonstrating the efficacy of febuxostat have included patients with renal impairment.[97]

In a patient with stage 3 chronic kidney disease in whom urate-lowering therapy is indicated, allopurinol 100 mg daily or febuxostat 40 mg daily should be initiated; after 2–4 weeks the doses should be increased to 200 mg or 80 mg daily, respectively, provided serum urate remains >6.0 mg/dL. Monitoring of serum urate should be continued every 2–4 weeks until it reaches the <6.0 mg/dL target, then at 6–12-monthly intervals thereafter. The patient should be assessed for any adverse reactions to the drug used.

How are patients with advanced gouty arthritis best managed?

Advanced (or chronic) gout usually develops after several years to a decade or more of acute intermittent gout, though patients may present with tophi as the initial clinical manifestation; in chronic gout, the joints are persistently swollen and uncomfortable between acute flares.[98] Subcutaneous tophi are the most characteristic lesion of advanced gout.[98] Chronic gout may result from lack of treatment or hyperuricemia poorly controlled with urate-lowering therapy.[99] Urate-lowering options for advanced gouty arthritis are allopurinol, probenecid, or febuxostat. Initiation of urate-lowering therapy, with reduction of serum urate to <6.0 mg/dL, can effect a good clinical response, with reduction of tophi and remission of acute attacks, even in patients with severe tophaceous gout.[33] Substantial morbidity is however asso-

FIGURE 8: Incidence of gout flares during urate-lowering therapy.



ciated with poorly controlled hyperuricemia and treatment-failure gout.[99] Febuxostat may have utility in patients who have developed advanced gout despite allopurinol therapy or those who have allopurinol intolerance or allergy, as it has demonstrated ability to reduce flares and resolve tophi.[75]

How should breakthrough flares of gouty arthritis in patients taking allopurinol be managed?

Despite anti-inflammatory prophylaxis, patients on urate-lowering medication may experience breakthrough flares of gouty arthritis; patients should be warned that gout flares may occur and that these should be treated promptly.[57] (**Figure 8**) Management of a gout flare in a patient receiving antihyperuricemic therapy is the same as for acute gout – the urate-lowering agent should not be discontinued or altered during an acute flare.[60]

What are the roles of new and emerging urate-lowering drugs in gout?

The traditional medication arsenal for controlling hyperuricemia is limited, and there are substantial gaps in patients with chronic kidney disease, allergies, and drug interactions. Febuxostat, the newly approved antihyperuricemic agent, provides an alternative to allopurinol, and is a valuable option in elderly patients, especially those with chronic kidney disease. Other urate-lowering drugs are in development Conversion of uric acid to allantoin, a more soluble and readily excreted form, is one alternative approach; this conversion is catalysed by uricase (urate oxidase, an enzyme lacking in humans), and various forms of the enzyme have been and are under investigation (**Table 3**).[105]

TABLE 3: Urate-lowering drugs currently in clinical trials

	Phase	*Mechanism*	*Reference*
Oxypurinol	II	Xanthine oxidase inhibitor	Anon, 2004[100]
Y-700	I–II	Xanthine oxidase inhibitor	Yamada et al, 2004[101]
Pegloticase	III	Pegylated urate oxidase	Baraf et al, 2008[102]
Uricase PEG20	II	Pegylated urate oxidase	Bomalaski et al, 2002[103]
RDEA806	I	Non-nucleoside reverse transcriptase inhibitor (NNRTI)	U.S. NIH, 2008[104]

SUMMARY

Gout is a growing problem that can cause substantial morbidity in the elderly population. For many years, there have been limited treatment options for controlling hyperuricemia, resulting in substantial treatment gaps, especially in patients with chronic kidney disease, those with intolerance or allergies, and patients needing to take medications that interact with urate-lowering agents. This has meant that treatment goals are often not achieved and disease progression occurs. Management in the elderly poses particular challenges owing to atypical presentation, age-related physiological changes, comorbidities, and multiple concomitant drug use. Febuxostat is likely to be a valuable additional therapeutic option, particularly in elderly patients, because of its demonstrated safety in patients with renal impairment and lack of association with hypersensitivity reactions.

In the elderly, management of gout includes instituting lifestyle changes, where possible removing medications that may be causing or exacerbating the problem, and using a therapeutic approach likely to be tolerated well by the elderly patient. The key goals of management of gout are to terminate acute flares with prompt therapy of appropriate dose and duration, and thereafter to control chronic hyperuricemia and tissue crystal deposition by lowering serum urate to <6.0 mg/dL while under the cover of anti-inflammatory prophylaxis. Monitoring serum urate to ensure that this target is reached is critical, as is monitoring for adverse events. Addressing comorbidities and cardiovascular risk factors in patients with hyperuricemia and gout is another important aspect of management. ■

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POST-TEST QUESTIONS

1. Which of the following statements is not correct?
   a. The incidence of gout in men and women aged 75–84 years is similar
   b. Prevalence of gout peaks in men at 75–84 years
   c. Over 6 million people in the USA have been affected by gout
   d. The prevalence of gout in men and women aged 75–84 years is similar

2. Hyperuricemia is defined as:
   a. Serum urate concentration above the upper limit of the normal range for the local population
   b. Serum urate >6.0 mg/dL
   c. Serum urate >6.8 mg/dL
   d. Serum urate >7.5 mg/dL

3. Which of the following statements is correct?
   a. Hyperuricemia usually results from overproduction of uric acid
   b. In the USA, metabolic syndrome is twice as common in patients with gout as in controls
   c. High intake of dairy protein is associated with increased risk of gout
   d. High intake of purine-rich vegetables is not associated with increased risk of gout

4. Which of the following is not a feature of gout in the elderly?
   a. Association with diuretic use
   b. Decreased incidence of tophi
   c. Polyarticular onset
   d. Localization of tophi on osteoarthritic nodes

5. Which of the following statements is correct?
   a. Maximum dose of an NSAID is recommended during the early stages of urate-lowering therapy to prevent acute gout flares
   b. Treatment of gout should not begin until the condition has been confirmed by joint aspiration
   c. Serum urate concentration rises during an acute attack of gout
   d. Tissue damage may persist during the intercritical phase

6. Which of the following is not potentially useful in the treatment of an acute attack of gout in the elderly?
   a. Topical ice
   b. Allopurinol
   c. Indomethacin
   d. Oral colchicine

7. Which of the following statements is not correct?
   a. If urate-lowering therapy is indicated, it should be initiated as soon as an acute gout attack has resolved
   b. Urate-lowering therapy is recommended in patients who have polyarticular acute gout attacks
   c. Probenecid is ineffective in patients with creatinine clearance <50 mL/min
   d. The aim of urate-lowering therapy is to reduce and maintain serum urate <6.0 mg/dL

8. Which of the following is not a possible limitation of allopurinol?
   a. Cutaneous rash
   b. Unsuitability for use in hyperuricemia resulting from overproduction of urate
   c. Hypersensitivity syndrome
   d. Requirement for reduced dosing in patients with chronic kidney disease

9. Which of the following statements is correct?
   a. In a 52-week trial, significantly more patients achieved serum urate <6.0 mg/dL with febuxostat 80 mg daily than with allopurinol 300 mg daily
   b. Dosage reduction is necessary when prescribing febuxostat to elderly patients with chronic kidney disease
   c. Caution is required when prescribing febuxostat with NSAIDs
   d. Febuxostat is contraindicated in patients who have experienced allopurinol hypersensitivity syndrome

10. Which of the following is not a potential barrier to effective control of gout in the elderly?
    a. Inadequate dosing of allopurinol
    b. Insufficient monitoring of serum urate levels
    c. Age-related decline in renal function
    d. The inability of urate-lowering agents to resolve established tophi in patients with advanced gouty arthritis

ANSWER AND EVALUATION FORM

September 1, 2009 – September 1, 2010

Answers: Refer to quiz. Circle ALL that apply for each question.

1.	A	B	C	D
2.	A	B	C	D
3.	A	B	C	D
4.	A	B	C	D
5.	A	B	C	D
6.	A	B	C	D
7.	A	B	C	D
8.	A	B	C	D
9.	A	B	C	D
10.	A	B	C	D

If you wish to receive acknowledgement for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation as verification of participation, and fax to: **(949)-824-3037 or Mail form to:**

Bonnie Carroll
Director Continuing Medical Education
University of California, Irvine School of Medicine
Building 802
Rm 120H
Irvine, CA 92697-4089

Fill in ALL information in order for your registration form to be processed.

First Name: _____ MI: _____ Last Name: _____

Title: _____

Address: _____

City: _____ State: _____ Zip: _____

Phone: _____ Fax: _____

Email: _____

Last 5 digits of SS# _____ or Medical License Number (Mandatory): _____

Specialty: _____

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Please answer the following questions by circling the appropriate rating:

1. Overall evaluation of the activity: **Excellent** **Very Good** **Good** **Fair** **Poor**
2. Quality of the educational content: **Excellent** **Very Good** **Good** **Fair** **Poor**
3. Was this activity responsive to your needs? **Yes** **No**
4. Was this activity relevant to your practice? **Yes** **No**
5. Did this activity increase your knowledge and/or skills in delivering patient care? **Yes** **No**
6. Were the following objectives met?
   - A. Summarize the prevalence of gout in older patients and factors which may contribute to both primary and secondary hyperuricemia in this age group
   - B. List the criteria for the staging of gout
   - C. Enumerate the risk factors and co-morbidities that can contribute to, and exacerbate, flares of gout in older patients
   - D. Optimize diagnostic testing to ensure maximal yeild from these tests
   - E. Consider the latest therapeutic options available for long standing gout and which are suitable for use in patients with renal and hepatic insufficiency

7a. In your opinion, were any presenters biased in their discussion of any commercial products or services? **Yes** **No**

7b. **Please elaborate:** _____

8a. Issues in cultural and linguistic competency (e.g. differences in prevalence, diagnosis, treatment in diverse population; linguistic skills; pertinent cultural date) were adequately addressed in this activity? **Strongly Agree** **Agree** **Neutral** **Disagree** **Strongly Disagree**

8b. Resources on cultural and linguistic competency have been included in your materials. How can we further meet your educational needs in this area?

_____

9. How will you change your clinical practice as a result of this activity? _____
10. Which topics were the most useful? _____
11. Which topics were the least useful? _____
12. Please suggest other topics that should be covered in future activities. _____
13. Other comments: _____

Degree: MD or DO: _____ Specialty: _____

Resident: _____ Other (please specify) _____