

Gout: new advances in the diagnosis and management of an old disease

Gout is a monosodium urate crystal deposit disease, occurring as a consequence of hyperuricemia. Very importantly, the formation of crystals is reversible and they slowly dissolve when serum urate levels became normal, so the disease can be considered curable. The identification of urate crystals in synovial fluid allows simple unequivocal diagnosis; diagnosis based on clinical features and hyperuricemia is often inaccurate, even if patients fit the American College for Rheumatology Classification Criteria. Several recent publications show that gout is frequently misdiagnosed, and management often falls below reasonable standards. The main aim of treatment is to dissolve the deposited crystals, freeing the patient of the disease; this is usually achieved by allopurinol, and new drugs will be available soon. Crystal deposit is silent but signaled by the occurrence of gouty attacks, for which treatment is effective, and can be avoided with adequate prophylaxis. Alterations related to the so-called metabolic syndrome (such as high blood pressure, insulin resistance, dyslipidemia, abdominal obesity and propensity to atherosclerosis) are often signaled by gout, and require proper attention.

KEYWORDS: gout ■ monosodium urate crystals ■ urate lowering therapy

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Learning objectives

Upon completion of this activity, participants should be able to:

- Describe the elements of the diagnosis of gout
- Identify the level of serum uric acid associated with clearance of urate crystals from joints
- Describe the use of medications to reduce serum uric acid levels
- Specify treatments to reduce gout-related inflammation

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The most evident manifestations of monosodium urate (MSU) crystal deposition – namely episodic and later persistent joint inflammation and tophi – were already recognized in antiquity, and the term gout was coined for these symptoms. The term gout has persisted until today, but the underlying crystal deposition has increasingly been recognized and gained a central position in the way we understand the disease, of which joint inflammation is only a consequence. Although it appears reasonable to include under the term gout all MSU crystal deposition – even if joint inflammation has not yet occurred – it remains unsettled as to whether we should restrict the term to its original meaning to refer to the manifestations of arthritis and visible/palpable tophi, or broaden its meaning to include in it the basic underlying MSU deposit with its different manifestations. In this article, we will consider this broader definition of gout.

The recent publication of guidelines on gout diagnosis and management by The European League Against Rheumatism (EULAR) [1,2] and quality-of-care indicators from the USA [3] outlines the current interest in gout. Most advances in the diagnosis and management of gout were carried out before the modern era of evidence-based medicine, and although the experience accumulated in gout diagnosis and treatment is large, the number of randomized trials is very small. Even so, most experts would agree that we currently understand the disease well, and have very effective treatments available.

Such a reassuring background would suggest that, with few exceptions, gout is no longer a problem anymore and that gouty patients can rest assured that their disease will be easily tackled. Surprisingly, clinical practice in gout lags far behind easily achievable goals; this lack of excellence can only be explained by a collective lack of interest by physicians at large [4]. There has been much interest in evaluating how gout is managed in the community in the last few years; this research has shown that inappropriate diagnosis based on the interpretation of clinical features and hyperuricemia [5,6] (a very traditional but inaccurate way of approaching gout diagnosis) and insufficiently careful use of available medications [5,7–9], in addition to poor follow up of the patients [7,10,11], have transformed gout for many patients into what it should never be: a chronic and persistent source of pain and infirmity. Care of gouty patients is centered in a primary care setting in many countries; quality of care seems to improve somewhat when dispensed by rheumatologists, even though results are still far from desirable [6,10].

Recent articles have brought attention to the problem of poor management and the need for action [4,12–14], but no specific plans are proposed. It seems as if rheumatologists are not heeding the signs of their bad management in gout, perhaps through lack of awareness, but more likely through a lack of interest in a disease perceived by many as minor (even though any physician who cares for gouty patients knows how severe this disease can be) and academically irrelevant. The burning question for rheumatologists at large is whether we are interested in caring for gouty patients. If we are, immediate action is mandatory, and the first necessary step is to seriously implement the application of the standards of management of gout at the same level of excellence that we demand in many other diseases under our responsibility. Implementing crystal analysis techniques in rheumatology units (most importantly in all training units, without exception) to guarantee the diagnosis of gout with unequivocal evidence, and to adhere to the available treatment guidelines (or develop new ones) are equally important actions. In fact, if we consider that rheumatologists should not be the physicians caring for gout, an alternative solution needs to be found for the numerous patients with the disease worldwide.

Diagnosing gout

■ Crystal identification

After the regular presence of MSU crystals in synovial fluid (SF) samples from inflamed gouty joints was reported by McCarty and Hollander [15], this has become the gold standard for the diagnosis of the disease [16,17]. Gouty arthritis has not been described in the absence of MSU crystals, nor have MSU crystals been found to cause any other condition. The technique of SF analysis is elegant and simple, and after a short period of training the results are consistent [18]. Crystal identification in SF is considered a part of most core curricula in rheumatology [201,202], but this learning appears to be frequently overlooked. Workshops on crystal identification at the EULAR Congress have been carried out regularly since 2002. Although MSU crystals can be seen by means of the regular microscope, they are strongly birefringent and more easily identified by means of a polarized microscope. To avoid confusion with the also very common calcium pyrophosphate dihydrate (CPPD) crystals, a first-order red compensator allows a distinction based on the strong negative birefringence of the MSU crystals and the weak positive birefringence of the CPPD crystals.

Those experienced in crystal analysis tend to feel that the always acicular MSU crystals and rhomboidal, parallelepipedic and acicular CPPD are difficult to mistake, the main identification problem arising when both crystals are present together, an unusual situation of little practical relevance and where familiarity with the crystals and the use of polarized filters and the compensator facilitates identification. In addition, the very strong birefringence of MSU crystals contrast sharply with the often absent or weak birefringence of CPPD [19,20].

A sample of all SF drained from undiagnosed arthropathies must be analyzed for crystals [1], since less 'typical' forms of gout (and also CPPD arthropathy) are not rare, and otherwise may pass unnoticed or mistaken for another condition. Even the diagnosis of patients with 'typical' gout should be based on crystal identification; at least until new evidence proves that we can accept such 'typical' clinical features as unquestionable.

Gouty patients are asymptomatic most of the time, but if patients have not received treatment to normalize serum uric acid (SUA) levels for a prolonged period of time, a definitive diagnosis is possible by the persistence of MSU crystals in SF fluid of asymptomatic joints that have been previously inflamed [21–23]; aspirating asymptomatic knees and first metatarsophalangeal (MTP) joints is a simple and well-tolerated procedure [24,25]. The reiterative absence of crystals may be used to exclude gout in patients with arthritis and hyperuricemia, and the presence of crystals in other arthritis may indicate either both diseases or a misdiagnosis. After successful SUA therapy has started, MSU crystals can still be found, but they finally disappear, sooner in gout of lesser duration [22]. In patients with palpable tophi crystals, can easily be obtained by needling them. Only rarely are MSU crystals sought in tissue samples; formalin dissolves the crystals [26], so if a biopsy is performed searching for MSU crystals, it has to be fixed in alcohol, or processed by freezing.

■ Limitations of clinical diagnosis

A precise diagnosis is the first step in order to appropriately manage any disease. As has been stressed above, an unequivocal diagnosis is easily achievable through MSU crystal identification; however, it is common practice to base diagnosis of gout on clinical findings and hyperuricemia. This approach involves a considerable amount of uncertainty, which clinicians would not accept if applied to other diseases. Recurrent episodes of acute arthritis of the first MTP joint (commonly

referred to as podagra) are considered as highly characteristic of gout, but podagra can have other causes such as infections [27,28], psoriatic arthritis [24] or other crystal arthropathies [29]; less specialized or unexperienced physicians can also mistake podagra for other problems at the first MTP joint or involving its surrounding tissues. On the other hand, over half of patients had a first gouty attack in a less typical location [30] – be it tarsum, ankle, knee or wrist – confounding physicians who can be unaware of the variety of clinical presentations of gout. When reviewing the different clinical presentations of gout, many case reports report gout in a wide variety of locations – arthritis of the temporo-mandibular joint [31], acromioclavicular joint [32], sternoclavicular [33], manubriosternal [34], sacroiliac [35], pubic symphysis [36] or hip joints [37], lumbar spine [38] or flexor tenosynovitis with carpal tunnel syndrome [39] – many of which can pass unnoticed to even the most expert of clinicians. Polyarticular, additive or less acute and more persistent presentations are not rare; all these presentations can be easily confused with other problems or may simply pass unnoticed. In all these cases, systematic MSU crystal investigation in SF samples obtained from all joints affected by undiagnosed conditions is essential in order to diagnose the whole spectrum of gouty arthritis.

Hyperuricemia can also be misleading. It is associated – as is gout – with the manifestations of the so-called metabolic syndrome (high blood pressure, insulin resistance, dyslipidemia, abdominal obesity) and is most frequently asymptomatic [40]. Only 0.5% of males with a SUA between 7 and 8.9 mg/dl (0.42–0.53 mmol/l) will develop gout within 1 year; this proportion rises to 4.9% if uric acid exceeds 9 mg/dl (0.54 mmol/l). [41]. In individuals with hyperuricemia, any articular manifestation can easily be mistaken for gout [42]. Conversely, the absence of high serum urate levels can make physicians disregard the diagnosis of gout. However, SUA levels can lower during acute attacks, even reaching normal values in many patients, owing to an increase in renal excretion [43–45]. In addition, gout attacks are frequent when starting urate-lowering therapy, or can occur at any time throughout treatment before crystals are dissolved – especially if no colchicine prophylaxis is administered. In all of these circumstances, the concurrence of normal uricemia with an acute monoarthritis can disorient the physician who relies on hyperuricemia to diagnose gout.

The American College of Rheumatology (ACR) criteria, published in 1977 in preliminary form as classification criteria for acute primary gout [46], have been repeatedly used to support the clinical approach to diagnosing gout; the criteria recognize the absolute value of the detection of MSU crystals for the diagnosis, but offer an alternative based on a combination of clinical analytical and imaging data. Of interest, the gold standard of gout diagnosis in Wallace's paper was clinical diagnosis, and only 50% of the patients with gout received a crystal diagnosis. No validation of the criteria had been attempted until recently. The validity of the ACR criteria – and also the Rome and New York criteria, two other sets of criteria based on clinical findings – were compared with MSU crystal identification in synovial fluid [47]. All sets of criteria performed quite poorly. In fact the ACR criteria had a sensitivity of 68% and a specificity of 78%, with both underdiagnosis and overdiagnosis needing addressing; discerning capacity was especially poor with calcium pyrophosphate arthropathy, but also with rheumatoid arthritis or osteoarthritis. Since gout left to its natural evolution implies ongoing inflammation and crystal deposition, but an erroneous diagnosis of gout implies lifelong urate-lowering therapy, this margin of error seems unacceptable. Those regularly caring for patients with gout should consider the need for the most rigorous approach to its diagnosis.

The accuracy of any clinical diagnosis is directly dependent on individual knowledge and experience, and therefore on the physician's degree of training, personal interest and clinical expertise. If rheumatologists – physicians with a special interest in arthritis and therefore in crystal arthritis – allow the diagnosis of gout to be performed on clinical grounds, while recognizing its inaccuracy, they authorize other carers with less clinical training in the field of musculoskeletal diseases to approach the diagnosis similarly, likely increasing the possibility of mistaking other joint conditions for gout. In the past 5 years, cases have been published in which the clinical diagnosis of gout was confused with septic arthritis [48], spondylodiscitis [49], rheumatoid arthritis [50] or tumors [51].

■ Diagnosing gout: future perspectives

Even though no alternative technique to SF aspiration can be recommended at present, ultrasound has been rapidly gathering evidence regarding its capacity to visualize

crystal deposits and other characteristic findings of gouty arthropathy, and supporters have vouched it could be the diagnostic technique of the future for gout. Several recent papers have described features that seem specific to gouty joints: hyperechoic enhancement of the outer surface of hyaline cartilage [52] (the so-called double contour sign), 'soft' and 'hard' tophi [53–55] and hyperechoic spots within the SF [56]. If ultrasound could identify patients with gout, it could prove an alternative method for diagnosing gout, in some cases forgoing the need for SF analysis. However, studies have generally included patients with long-standing, widespread disease; the reliability of ultrasound in patients with a first attack of gout and limited deposits, and its performance when compared with the gold standard of crystal identification, remain to be established before its use can be upheld in clinical practice.

Management

The first step for the proper management of gout is to establish an unequivocal diagnosis. Lack of recognition of gout owing to inappropriate evaluation, or treatment of other conditions as gout are both easily avoidable if patients are diagnosed by MSU crystal identification [1,3]. Proper management of gout is currently perceived by the medical community as problematic, as shown by the number of recently published standards and recommendations on the subject [1,16,57–60].

■ Aims of treatment

When planning the treatment of a patient with gout, several aims have to be independently considered. Gout is a reversible MSU crystal deposit disease; the normalization of SUA levels results in the dissolution of the crystals. The primary aim of the treatment of gout is to eliminate the urate crystals; they are the cause of the disease and with their disappearance joint inflammation can not occur and the disease can be considered cured (although SUA needs to be maintained in the normal range indefinitely to avoid formation of new crystals and the return of gout). An important aim is treatment of the episodes of joint inflammation; these may occur while MSU crystals remain in the joint. Bouts of arthritis can occur at the clinical presentation of the disease, after the start of SUA therapy – until crystals dissolve – and indefinitely in patients improperly treated (in whom SUA levels persistently below 6 mg/dl are not achieved) or left untreated. The prophylaxis of inflammatory episodes in joints still containing MSU crystals is another

important aim. These episodes are avoided by drugs that reduce the mild subclinical inflammation related to the presence of MSU crystals in asymptomatic joints. Finally, causes of gout should be evaluated and other conditions associated with gout, of which the most common is the metabolic syndrome or its components such as arterial hypertension, hyperlipidemia, obesity or glucose intolerance, should be recognized and treated. Lack of compliance with the treatment is reported to be a common cause of treatment failure in patients with gout. Adequate explanation of the aims of the treatment to the patient is an essential part of the management of gout. Patients must understand that dissolution of the urate crystals is the main goal of the treatment, and that the risk of gouty attacks will completely disappear if they are compliant.

■ Reducing uricemia to eliminate urate crystals

The primary objective of SUA-lowering therapy is to eliminate the urate crystals from joints and other tissues. The disappearance of tophi and cessation of gouty attacks as a result of the normalization of SUA levels were noted over 50 years ago [61]. More recent data have shown that MSU crystals disappear from previously affected gouty joints after adequate SUA-lowering therapy [62]. Different values have been given as the upper level of the normal range for SUA levels; reduction of SUA levels below 6 mg/dl (0.36 mmol/l) has been shown to result in crystal disappearance from the joints [63], and lower SUA levels result in faster reduction of the size of tophi [64,65], as probably occurs with the crystals deposited in joints and tissues. According to these data, SUA levels should be reduced to at least under 6 mg/dl, and quite likely, the lower the levels attained, the sooner the crystals will be cleared. The time of disappearance of MSU crystals from signal joints correlates well with the total duration of gout measured from the first attack. Of practical interest, nine out of ten signal joints of patients with gout of less than 10 years duration were free of crystals after 1 year of SUA-lowering therapy, and the remaining one by 18 months [22]. Interestingly, the patients included in this study achieved very low SUA levels; so the lower the better.

There is no general agreement on the right time after the first attack of gout to start SUA-lowering therapy. Recommendations have varied from very early initiation to not starting this therapy until the gout is severe, as judged by number of attacks or presence of chronic arthritis, tophi,

radiological lesions or uric acid renal calculi. When deciding the right time to initiate SUA-lowering therapy it is worth considering that crystals can be found in SF samples obtained from never-inflamed joints of gouty patients [23], and deposits of crystals have recently been described in periarticular structures of patients with asymptomatic hyperuricemia [66]. We lack a practical way of estimating the magnitude of crystal deposits at the time of the first attack of gout, and although in some patients the signaling first attack may appear shortly after the start of crystal deposition, in others the deposit of crystals is revealed quite late by the presence of tophi or by gout with a polyarticular start [67] – which may be more common in females [68] – both indicative of quite heavy deposits at the time of the initial clinical presentation. It is also worth considering that the recommendation of a delayed start of the SUA treatment is made on the assumption that MSU crystal deposition in joints and tissues appears innocuous both for the joint and for the patient. MSU crystals deposit in the surface of cartilage [55] with little apparent damage; joint erosions result from intraosseous tophi [69] indicating a less than minor crystal deposit. MSU crystals in joints during the asymptomatic periods interact quite heavily with cells [70], resulting in a modest persistent inflammation [23,71] with limited local consequences. More worrisome is the recent identification of gout as an independent risk factor for myocardial infarction [72,73], the level of this association rising with the severity of gout [74]. This may relate to the MSU crystal-associated inflammation both during the attacks and the persistent subclinical joint inflammation during intercritical periods [23,71]. Atherosclerosis in this setting may be favored by this persistent inflammation [75,76], as occurs in rheumatoid arthritis and systemic lupus erythematosus where the risk for atherosclerotic cardiovascular disease is also increased; other possible links between gout and atherosclerotic cardiovascular disease have also been proposed [77]. Gout is a reversible deposit disease; the earlier the treatment starts, the sooner the patient will be free of crystals [22]; the relationship between gout and myocardial infarction may be an added reason to consider earlier treatment, at least in patients at risk. Despite these arguments, the best time to start SUA-lowering treatment remains uncertain. After crystals have disappeared from the joints SUA levels should be maintained within the normal range to avoid *de novo* formation of urate crystals, and with them the possibility of reappearing gouty attacks [78–80].

The best method of ascertaining that MSU crystals have disappeared from the joints remains undetermined. Measuring total body urate by nuclear medicine or sampling signal joints until crystal disappearance [22] have been the two possibilities considered. Sonography may show the disappearance of gross joint deposits. In any case, since SUA levels in gouty patients are to be kept within normal values indefinitely, the need to ascertain the disappearance of crystals has more value as an end point for controlled clinical trials than for the attention of individual patients.

For all SUA-lowering drugs it is an often-accepted recommendation not to initiate treatment until the gout attack has fully recovered, since reduction of SUA by drugs is a well-recognized trigger for gout flares, and the initiation or increase in dosage of a SUA-lowering therapy in gouty patients frequently results in a gouty attack if prophylactic colchicine is not co-administered. In patients receiving very active SUA-reducing drugs, such as uricase, the gout flare induced by the drug can be particularly intense and polyarticular [81]. It remains uncertain what breaks the equilibrium between cells and MSU crystals that exist during the inter-critical periods: initiation of urate-lowering therapy may result in dissolution of the superficially located crystals, which may fall into the joint cavity, but formation of new crystals owing to a rise in SUA levels secondary to dietary over-indulgence – which patients often recognize as a trigger – is another possibility.

Allopurinol

Allopurinol is currently the mainstay SUA-lowering drug. It is widely available, has been extensively used, is inexpensive and for most gouty patients is a safe and effective option. It is a purine analogue that competitively inhibits xanthine oxidase, the enzyme that degrades hypoxanthine and xanthine to uric acid, reducing the amount of uric acid produced by purine degradation. Allopurinol is rapidly and extensively metabolized to oxypurinol, and the hypouricemic efficacy of allopurinol is largely due to this metabolite [82]. The drug is often reported to fail in attaining SUA levels below the target of 6 mg/dl (0.36 mmol/l) needed to dissolve MSU crystals and deplete the deposits, and these patients may be taken as refractory to allopurinol. However, most often this failure is due to poor dosing, since too often 300 mg/day is used as a fixed dose even though the dose can be raised up to a maximum of 800 mg/day according to the drug label [83], and a dose of

400–600 mg is necessary for a sufficient reduction of SUA levels in a substantial number of patients. It is this fixed dose of 300 mg (or even lower in renal impairment) that has been used for comparison with newly introduced drugs in randomized, controlled trials [84–86]. In a controlled trial a 300 mg/day dose of allopurinol resulted in a SUA level below 5 mg/dl (0.3 mmol/l) in only 21% of the patients, but inclusion was restricted to patients with high baseline SUA levels, above 8 mg/dl (0.48 mmol/l). In another trial, SUA levels below 6 mg/dl were attained by 53% of the subjects; when the dose was raised to 450 or 600 mg/day, all patients attained the target levels [87]; in this paper the average allopurinol dose to achieve urate control was close to 400 mg/day overall. In another study, 300 mg daily of allopurinol resulted in SUA levels below 6 mg/dl in only 23% of the patients, and this figure increased to 78% when 600 mg was administered [88]. In another trial, 300 mg/day of allopurinol resulted in a reduction of SUA levels below 5 mg/dl (a reasonable target keeping in mind that the aim of allopurinol administration is to eliminate urate crystal deposits, and that elimination appears more rapid if lower SUA levels are attained) in only 24% of the patients [89]. Taken together, these data show that the dose of 300 mg/day of allopurinol is frequently insufficient to adequately reduce SUA levels, but that properly dosing allopurinol is likely to result in SUA levels below 6 mg/dl in a majority of patients. Trials tailoring the allopurinol dose until the desired SUA level (or true failure) is achieved are still needed; this appears especially important owing to the imminent introduction of newer drugs aimed, among others, at those patients whose raised SUA levels appear uncontrollable by allopurinol, and we should assure that this lack of control is not due to insufficient dosing. A common cause of allopurinol failure is lack of compliance by the patients [90–93], which may in part result from lack of understanding by the patients of the aim pursued by this drug, that is, dissolving the MSU crystals and eliminating the disease.

Allopurinol dose requires correction according to renal function, since levels of oxypurinol, the main metabolite of allopurinol, relates to the glomerular filtration rate [94]. Recently published standards for quality care recommend dose reductions of allopurinol and avoidance of NSAIDs in patients with plasma creatinine above 2 mg/dl (177 μ mol/l) or creatinine clearance below 50 ml/min [3]. Allopurinol dose adjustment to renal function is also recommended by

the recent EULAR guidelines to avoid toxicity [1]. Adaptation of allopurinol dose can be based on the creatinine clearance [95] or estimation of the glomerular filtration by means of the Cockcroft–Gault equation [96]. Non-evidence-based guidelines exist for allopurinol estimated maintenance doses based on creatinine clearance (TABLE 1). However, adjusting allopurinol according to these guidelines does not provide adequate control of hyperuricemia in many patients with gout [97]. In addition, no increase in adverse reactions to allopurinol was seen in patients who received higher maintenance doses than those recommended according to creatinine clearance [99]. Therefore, for this group of patients higher doses may be needed and a dose titration above doses recommended by the guidelines, with close monitoring of the benefits and risks of the therapy, has been suggested [97]. Of particular importance, reduction of SUA has been found to improve renal function in both nongouty [100] and gouty patients with renal insufficiency [101,102], and also to reduce blood pressure in adolescents with hypertension [103].

Toxicity to allopurinol is not rare, and the hypersensitivity syndrome remains a serious and potentially lethal hazard [104]; the term drug rash with eosinophilia and systemic symptoms (DRESS) syndrome has recently been used to describe an entity presenting with similar features [105]. Allopurinol has also been reported as the most common cause of the Stevens–Johnson syndrome [106]. For mild cases of the allopurinol hypersensitivity syndrome, desensitization is an option [107], although the scheme of desensitization has not been critically evaluated. Azathioprine is also metabolized by xanthine oxidase. Allopurinol interferes in its metabolism, and their co-administration results in higher levels of azathioprine, which can result in toxicity. The general approach to both allopurinol hypersensitivity and refractoriness generally requires the use of alternative drugs.

Uricosuric drugs

The so-called uricosuric drugs (which work by inhibiting the urate transporter URAT1 at the tubules, thus raising the renal clearance of urate) are valid options if allopurinol is problematic. Since hyperuricemia in a majority of gouty patients is due to lowered renal clearance of uric acid [108], the use of uricosuric drugs is attractive. In 2003, benzbromarone was withdrawn by Sanofi–Synthelabo, after reports of serious hepatotoxicity, although it remains on the market in some countries through other drug

Table 1. General maintenance allopurinol dose, corrected by renal function.

Creatinine clearance (ml/min)	Allopurinol dose (mg)
140	400 daily
120	350 daily
100	300 daily
80	250 daily
60	200 daily
40	150 daily
20	100 daily
10	100 every 2 days
0	100 every 3 days
Hemodialysis (dialysis 2–3 times per week)	300 shortly after each dialysis session

These are maintenance doses; cautious increases can be essayed in patients not reaching serum uric acid target levels and tolerating the actual dose well [97,98]. A maximum of 800 mg daily can be used according to the drug label [83], at least in patients with normal renal function [98].

companies, and in Europe it remains available for restricted use in several countries. The withdrawal prompted a literature review that found that benzbromarone has no more toxicity than allopurinol or colchicine [109], and the withdrawal may not be in the best interest of the patients [110]. The treatment of patients refractory or intolerant to allopurinol remains the main indication [111]. It can be used in patients with mild-to-moderate renal insufficiency (creatinine clearances above 20 ml/min) [112], and has been a successful option for transplanted gouty patients [113,114]. In a larger series of kidney transplant patients treated with benzbromarone – a very similar drug to benzbromarone, now withdrawn from the market – the drug was proved to be superior to allopurinol in this setting [115]. A typical starting dose of benzbromarone would be 50 mg daily, to be increased in steps of 50 mg to the required maintenance dose (50–200 mg daily). In a recent trial, gouty patients who have not achieved SUA levels below 5 mg/dl (0.3 mmol/l) after receiving 300 mg/day of allopurinol were treated with 200 mg daily of benzbromarone, and the target SUA below 5 mg/dl was attained by 22/24 patients (92%). Another arm in the same study treated similar patients failing 300 mg/day of allopurinol with probenecid 2000 mg/day, and the target SUA levels were attained in 20/31 patients (65%) [89].

Of the older hypouricemic drugs, probenecid or sulfinpyrazone can be used in these patients if available. In patients with a history of renal calculi, uricosuric drugs have to be used cautiously, alkalizing the urine and increasing the ingestion of fluids, but only if there is no other rational option available. In difficult allopurinol ‘refractory’ patients, the combined use of allopurinol, which decreases the total amount

of urate formed, and a uricosuric drug, which by raising the renal urate clearance decreases further the SUA levels, is often effective and worth trying.

Febuxostat

New drugs to reduce SUA levels will be available soon: febuxostat is a nonpurine selective inhibitor of xanthine oxidase, which is orally administered and undergoes hepatic metabolism, with approximately half of the administered drug excreted in the stool and the remainder appearing in the urine [116]. Short-term pharmacokinetic studies performed in nongouty subjects with mildly impaired renal function [117] suggest that dose adjustment may not be required in these patients; there is no experience in patients with more severe renal dysfunction or in dialysis. Febuxostat in doses of 120 mg/day reduced SUA levels to less than 6 mg/dl (0.36 mmol/l) in 62% of patients (53% in those receiving 80 mg/day) [85]. The high SUA levels (8 mg/dl [0.48 mmol/l]) required to enter the study may partially explain the insufficient results. In a more recent trial, in which inclusion criteria also requested SUA levels above 8 mg/dl, higher percentages of subjects treated with febuxostat 80 mg (48%), 120 mg (65%) and 240 mg (69%) attained the primary end point of last 3-monthly serum urate levels below 6.0 mg/dl compared with allopurinol 300 mg/day (22%) or placebo (0%) [86]. The fixed low doses of allopurinol used as a comparator in these trials does not allow conclusions to be drawn regarding a possible superiority of febuxostat over allopurinol. It remains possible that properly titrated doses of allopurinol could yield comparable SUA levels to those achieved by titrated febuxostat. Safety of febuxostat remains a matter of concern since withdrawals due to side effects were more common in febuxostat- than in allopurinol-treated patients, mainly due to rash and abnormal liver function studies in one of the trials, where four deaths were also reported in subjects taking febuxostat versus none in those on allopurinol, although the difference was not statistically significant [85]. In the more recent trial, the adverse events rates were reasonably similar for both drugs tested [86]. Febuxostat appears a good drug for those patients with intolerance to allopurinol, and probably for those with renal failure.

Uricase

In all mammals except man and higher primates, which lost functional uricase through mutations [118,119], uricase degrades uric acid

to allantoin, which is soluble and easily eliminated. In humans, uricase is a very effective way of preventing and treating tumor lysis syndrome and SUA levels as low as 0.78 ± 0.4 mg/dl (0.05 mmol/l) after 4 h of administration can be achieved [120]. Rasburicase, a recombinant uricase, has been successfully used in unusually severe cases of gout [81,121–124]; a monthly dose of rasburicase appears to offer an effective option, though the number of infusions is limited by tolerance. In addition, the sharp SUA reduction often results in severe gouty attacks in these patients, despite proper prophylaxis [81]. At present, a pegylated uricase (in order to increase the half-life and decrease the immunogenicity of the drug) is under development for treatment of difficult gout [125]. These drugs appear to be able to deplete urate deposits at a faster rate than currently available drugs [65]. The proper place of these drugs in the management of gout will become established as we gain experience with them.

Other drugs

Both losartan and clofibrate have a modest and probably transient SUA level-reducing effect. They can be useful co-adjuvants in the management of gouty patients, who may also benefit from their effect in reducing blood pressure and lowering lipids.

■ Treatment of gout-related inflammation

Gouty attacks result from a disturbance of the equilibrium attained between cells and crystals in the joint cavity during the usually long intercritical periods, during which their interaction results in mild subclinical inflammation [23,71]. The resolution of an attack indicates that this equilibrium has been regained. If left untreated, gouty attacks subside spontaneously in several days or weeks; drugs with anti-inflammatory properties, such as NSAIDs and glucocorticoids, hasten the process and produce a rapid relief of symptoms. Colchicine is also used for the treatment of acute gout. Since the major advances in gout treatment occurred before the introduction of randomized, controlled trials, very few studies have been conducted to critically evaluate the different alternatives [126], so the selection between the different therapeutic options to treat gout inflammation remains empirical and controlled studies would be welcomed. It is generally accepted that treatment early after the start of an attack results in faster resolution.

NSAIDs

All NSAIDs that have been evaluated for the treatment of acute attacks of gout have shown efficacy. NSAIDs are considered a convenient and well-accepted therapeutic option and the choice of the specific NSAID is largely a matter of personal preference. It appears reasonable to utilize full doses of the selected drug unless contraindications are present. Indomethacin has been traditionally considered as a particularly effective agent. Selective inhibitors of cyclooxygenase-2 are the most recently introduced agents of the group, and in a randomized, controlled clinical trial etoricoxib 120 mg once a day has been found to be as effective as indomethacin, 50 mg three times a day [127]. A recent interesting randomized trial has shown that naproxen 500 mg twice a day is as effective as prednisone 35 mg daily [128]. The well-known side effects of the group – gastrointestinal, cardiovascular and renal – are the major limitation for the use of NSAIDs in acute gouty arthritis, which often strikes elderly patients and those with comorbidities. Gouty attacks very rarely constitute a major health problem, and safer alternatives to NSAIDs have to be seriously considered when safety is a concern.

Glucocorticoids

A short course of systemic glucocorticoids (such as 30–40 mg of prednisone during 2–4 days with a rapid taper off) [129,130] or adrenocorticotropic hormone [131] have both been found to be effective. As mentioned above, prednisone (35 mg daily) has been found to be equally effective as naproxen (500 mg twice a day) [128]. Short courses of glucocorticoids may be followed by a rebound attack of gout. This can be avoided by co-administration of prophylactic doses of colchicine (0.5–1.5 mg/day) from the start of the glucocorticoid treatment. Intra-articular glucocorticoids, even in small doses [132], are effective, may minimize the systemic effects of these drugs and are safe if joint infection has been excluded [133].

Colchicine

Colchicine has a long tradition in the treatment of gout; formerly, response to colchicine has been used as a diagnostic aid for gout. In a controlled study, colchicine resulted in very frequent side effects [134], but the doses used were higher than those generally used today. A very recent large multicenter randomized clinical trial in gouty patients with normal renal function has showed equivalent efficacy in the treatment of acute gout

flares of 1.8 mg of colchicine (1.2 mg followed by 0.6 mg in 1 h) versus 4.8 mg of colchicine (1.2 mg followed by hourly doses of 0.6 mg for 6 h), with significant less gastrointestinal toxicity of the lower dose [135]. The EULAR consensus guidelines also proposed lower doses of colchicine (a maximum of three tablets of 0.5 mg in the first 24 h) for acute gout, to maintain efficacy while reducing its debilitating side effects. Colchicine toxicity and its possible drug interactions remain a concern [136]; besides the acute gastrointestinal effects, myelotoxicity and myotoxicity after prolonged use as prophylactic therapy may occur, most often in older patients with comorbidities [137]. Though finding the optimal dose is still a subject of research, doses of 0.5 mg twice (in older persons) or even three-times daily (lowering to once daily in case of renal or hepatic abnormalities) appear reasonable. Schemes with more frequent dosages are obsolete and frequently lead to substantial toxicity: nausea, abdominal complaints, diarrhoea and vomiting. Colchicine has recently been reviewed extensively elsewhere [136].

The problem of the management of ‘refractory’ gout inflammation (often long-neglected and polyarticular) has only received anecdotal attention. A combination of a medium dose of systemic glucocorticoids and intra-articular glucocorticoid injection of the most severely inflamed joints is worth trying. In one of these ‘unresponsive’ patients, anti-TNF- α has been reported to be effective [138]. MSU crystals trigger IL-1 release, via innate immune pathways and the ‘inflammasome’ complex. Based on this rationale, ten patients with acute difficult gout were successfully treated with the IL-1-inhibitor anakinra [139]. Before employing these therapeutic modalities at a larger scale, there is a need to better characterize persistent, poorly responsive gouty inflammation and determine its response to more standard, well-known and cheaper therapies.

■ Prophylaxis of recurrent gouty attacks

While MSU crystals remain in the joints, gouty patients may be stricken by gouty attacks; the aim of prophylactic treatment is to keep patients free of them. Attacks at the start of gout tend to be infrequent. In the absence of treatment the attacks tend to become more frequent, often more severe and can spread to previously unaffected joints. The most appropriate time to start prophylactic treatment has not received critical attention. It should always be initiated at the time of the introduction of a urate-lowering drug

to try to avoid the acute attack that frequently accompanies this treatment. At times, a first attack may not be followed by subsequent bouts for an extended period of time, and if hypouricemic treatment is not started, prophylaxis may be withheld after discussion of the issue with the patient. When attacks have become frequent and bothersome, SUA prophylaxis should be given along with SUA-lowering therapy.

In an early trial, patients receiving 1.5 mg/day of colchicine with probenecid therapy showed a significant decrease in the number of gout flares when compared with patients receiving only probenecid [140]. A retrospective analysis also suggests that the daily administration of 0.5–1.5 mg of colchicine in most cases avoids further attacks of inflammation [141]. Colchicine likely works, at least in part, by settling the baseline subclinical inflammation of the gouty joints to a lower, more stable level [69], and also by inhibiting neutrophil adhesion by diminishing expression of E-selectin on endothelium [142]. The optimal length of prophylactic treatment after the initiation of hypouricemic therapy remains undefined. A recent report suggests that prophylaxis should last for at least 6 months (which is the total duration of that study) [143]; in this trial patients received 1.2 mg daily and in 40% of them, the dose had to be reduced due to diarrhea. Data from another trial demonstrate that 2 months of prophylaxis is too short [85]. After initiation of SUA-lowering therapy gouty attacks may still occur until the joint is freed of crystals, and we think that for complete avoidance of attacks, colchicine therapy should be maintained until complete dissolution of the crystals. On the other hand it has been noted that after prolonged successful SUA-lowering therapy gouty attacks became rarer [144,145]; this may relate to the decrease in concentration of MSU crystals in SF that results from SUA-lowering therapy [22]. These features would justify a reasonably short prophylaxis after stable and successful SUA-lowering therapy has been instituted. In our practice we have found that for the few patients who are intolerant even to small daily doses of colchicine, an every-other-day schedule can be attempted. In addition, a small dose of a NSAID, such as naproxen 250–500 mg daily or indomethacin 25 mg daily, may be an appropriate alternative. Rare patients with long-standing severe gout may continue with gouty attacks despite prophylaxis with colchicine and a small dose of NSAID. For these patients a small dose of prednisone (5–7.5 mg/day) may be necessary some time after the initiation of SUA-lowering

therapy. New studies are looking at the possibility of using drugs that block IL-1 as prophylactic therapy, although its use would appear restricted to quite exceptional occasions.

■ Dietary & lifestyle factors, & medication

Throughout history, gout has been popularly associated with overindulgence in alcohol and food associated with wealth [146]. In fact, the prevalence of gout has increased in recent decades in most countries [147], and the rise in developing countries has been at least partially related to a change from traditional to westernized diets [148]. Hyperuricemia and gout are so closely associated to the so-called metabolic syndrome that hyperuricemia has been considered as an element of the metabolic syndrome [149,150], where hyperuricemia results mainly from a decreased renal clearance of urate [151]. Any diagnosis of gout must therefore be followed by a thorough evaluation for the presence of other elements of the metabolic syndrome, namely high blood pressure, insulin resistance, dyslipidemia and abdominal obesity, and attention to comorbid conditions is considered a key issue in recently published recommendations on gout management [1]. In addition to being associated with the metabolic syndrome, gout has now been identified as an independent cardiovascular risk factor, increasing the risk of myocardial infarcts [72,73], fatal coronary heart disease and the risk of death from cardiovascular causes [73]. The level of the association rises with an increasing severity of gout [74].

In hyperlipidemic patients a hypocaloric diet not only decreases lipid serum levels, but also serum urate levels through an increase in urate renal clearance [152]. No doubt the benefits of appropriate lifestyle changes would go far beyond their effect on gout. The relationship between lifestyle changes, diet and gout has recently been extensively reviewed [153–156]. In addition to the classic recommendations of reduced intake of purine-rich foods (such as anchovies, herring and organ meat) and alcohol (especially beer and spirits), sugar-sweetened soft drink consumption should be kept to a minimum [157,158]. By contrast, diet soft drinks, coffee or dairy products seem to have no effect, or even a slight beneficial effect, on serum urate levels [159–161].

SUA-increasing medication

Diuretics, by reducing renal clearance of urate, may induce hyperuricemia and gout. Their recent introduction may trigger gouty

attacks [162]. On the other hand, in a controlled, community-based study on development of gout in patients receiving diuretics, gout was found to associate with the cardiovascular conditions for which the diuretics were prescribed, which associate to lower clearance of urate by the kidneys, as diuretics do, rather than to the diuretic itself [163]. In another study, however, odds ratios of recurrent gout attacks were 3.2 and 3.8 for use of thiazide and loop diuretics, respectively [162]. The association between diuretics and gout warrants further studies [164]. In addition to diuretics, decreased fractional excretion of urate can also be the result of the ingestion of drugs such as ciclosporin [24] and low-dose aspirin [25]. Other SUA-increasing drugs are mycophenolate mofetil, pyrazinamide, ethambutol, nicotinic acid and cytostatic agents [165].

Future perspective

The future for gouty patients largely depends on whether the best standards of management for gout are finally widely applied, since we already have excellent means for unequivocal diagnosis

and very effective treatment in most patients. The situation of gout is unusual in medicine: while in other conditions considered severe a search for solutions is constant, and when found eagerly applied, in gout the solutions and recommendations already exist, but surprisingly their application is hampered by current habits of practice. Gout is the result of MSU crystal deposit in joints and tissues, a consequence of hyperuricemia. The deposit is fully reversible by reducing SUA levels to normal values, often requiring lifelong treatment. Such characteristics require an unequivocal diagnosis, which is possible by MSU crystal identification in synovial fluid, a technique that requires previous training in techniques of arthrocentesis and SF analysis. To gauge the magnitude of the MSU crystal deposit as a more direct means of determining the severity of gout is becoming feasible and may be an area of research in the near future. In addition, to better assess the impact of MSU crystal deposit and gout in the general health, and more specifically in atherosclerosis and its repercussions in the cardiovascular system, is an area open to research.

Executive summary

- Gout is unequivocally diagnosed through monosodium urate crystal identification; clinical diagnosis is too inaccurate.
- The aim of therapy is to dissolve all deposited urate crystals by reducing serum urate levels.
- Allopurinol is the current mainstay urate-lowering therapy. Doses should be titrated upwards before refractoriness is considered.
- New drugs – xanthine oxidase inhibitors such as febuxostat or uricase analogues – show promising results and will soon be available.
- There is a need for improved clinical practice to meet current optimal management standards.

Bibliography

Papers of special note have been highlighted as:

▪ of interest

▪▪ of considerable interest

- 1 Zhang W, Doherty M, Bardin T *et al.*: EULAR evidence based recommendations for gout – Part II management: report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann. Rheum. Dis.* 25, 1301–1311 (2006).
- 2 Zhang W, Doherty M, Pascual E *et al.*: EULAR evidence based recommendations for gout – Part I diagnosis: report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann. Rheum. Dis.* 65, 1312–1324 (2006).
- 3 Mikuls TR, MacLean CH, Olivieri J *et al.*: Quality of care indicators for gout management. *Arthritis Rheum.* 50, 937–943 (2004).
- 4 Pascual E, Sivera F: Why is gout so poorly managed? *Ann. Rheum. Dis.* 66(10), 1269–1270 (2007).
- 5 Roddy E, Zhang W, Doherty M: Concordance of the management of chronic gout in a UK primary-care population with the EULAR gout recommendations. *Ann. Rheum. Dis.* 66(10), 1311–1315 (2007).
- 6 Perez-Ruiz F, Pascual E, Carmona L, De Miguel E, Ureña I, Gonzalez-Gay M: Diagnosis of gout in the rheumatology, hospital-based setting lies far from that recommended: results from the GEMA (gout evaluation of management) study. *Ann. Rheum. Dis.* 67(Suppl. 2), 246 (2008).
- 7 Singh J, Hodges J, Toscano J, Asch S: Quality of care for gout in the US needs improvement. *Arthritis Rheum.* 57(5), 822–829 (2007).
- 8 Mikuls T, Farrar J, Bilker W, Fernandes S, Saag K: Suboptimal physician adherence to quality indicators for the management of gout and asymptomatic hyperuricaemia: results from the UK General Practice Research Database (GPRD). *Rheumatology* 44, 1038–1042 (2005).
- 9 Mikuls T, Curtis J, Allison J, Hicks R, Saag K: Medication errors with the use of allopurinol and colchicine: a retrospective study of a national anonymous internet-accessible error reporting system. *J. Rheumatol.* 33, 562–566 (2006).
- 10 Perez-Ruiz F, Carmona L, De Miguel E, Ureña I, Pascual E, Gonzalez-Gay M: Variability in the treatment of gout: results from the GEMA audit of clinical practice. *Ann. Rheum. Dis.* 67(Suppl. 2), 246 (2008).
- 11 Annemans L, Spaepen E, Nash C, Bonnemaire M, Gilbert T, Malier V: Medical management of chronic gout in the UK and Germany. *Ann. Rheum. Dis.* 65(Suppl. 2), 430 (2006).
- 12 Sundy JS: Gout management: let's get it right this time. *Arthritis Rheum.* 59, 1535–1537 (2008).
- 13 Edwards NL: Treatment-failure gout: a moving target. *Arthritis Rheum.* 58(9), 2587–2590 (2008).
- 14 Terkeltaub R: Learning how and when to employ uricase as bridge therapy in refractory gout. *J. Rheumatol.* 34(10), 1955–1958 (2007).

- 15 McCarty DJ, Hollander JL: Identification of urate crystals in gouty synovial fluid. *Ann. Intern. Med.* 54, 452–460 (1961).
- 16 Terkeltaub RA: Clinical practice. Gout. *N. Engl. J. Med.* 349, 1647–1655 (2003).
- 17 Chen Lx, Schumacher HR: Current trends in crystal identification. *Curr. Opin. Rheumatol.* 18(2), 171–173 (2006).
- 18 Lumbreras B, Pascual E, Frasquet J *et al.*: Analysis for crystals in synovial fluid: training of the analysts results in high consistency. *Ann. Rheum. Dis.* 64(4), 612–615 (2005).
- **After a short training period for the analysts, identification of monosodium urate and calcium pyrophosphate dihydrate (CPPD) crystals in synovial fluid is a consistent technique.**
- 19 Ivorra J, Rosas E, Pascual E: Most calcium pyrophosphate crystals appear as non-birefringent. *Ann. Rheum. Dis.* 58, 582–584 (1999).
- **Important clue for the differentiation of monosodium urate and CPPD crystals**
- 20 Pascual E, Jovani V: Synovial fluid analysis. *Best Pract. Res. Clin. Rheumatol.* 19, 371–386 (2005).
- 21 Pascual E, Batlle-Gualda E, Martínez A *et al.*: Synovial fluid analysis for diagnosis of intercritical gout. *Ann. Intern. Med.* 131(10), 756–759 (1999).
- 22 Pascual E, Sivera F: Time required for disappearance of urate crystals from synovial fluid after successful hypouricemic treatment relates to the duration of gout. *Ann. Rheum. Dis.* 66(8), 1056–1058 (2007).
- **Urate-lowering therapy results in disappearance of urate crystals from synovial fluid, a direct proof of the complete reversibility of urate deposit. The time required for disappearance is longer in gout of longer duration.**
- 23 Pascual E: Persistence of monosodium urate crystals, and low grade inflammation, in the synovial fluid of untreated gout. *Arthritis Rheum.* 34, 141–145 (1991).
- 24 Sivera F, Aragón R, Pascual E: First metatarsophalangeal joint aspiration using a 29-gauge needle. *Ann. Rheum. Dis.* 67, 273–275 (2008).
- 25 Pascual E, Doherty M: Aspiration of normal or asymptomatic pathological joints for diagnosis and research – indications, technique and success rate. *Ann. Rheum. Dis.* 68(1), 3–7 (2009).
- 26 Simkin PA, Bassett JE, Lee QP: Not water, but formalin, dissolves urate crystals in tophaceous tissue samples. *J. Rheumatol.* 21, 2320–2321 (1994).
- 27 Velilla-Moliner J, Martínez-Burgui J, Cobeta-García JC, Fatah-Bandpey ML: Podagra, is it always gout? *Am. J. Emerg. Med.* 22(4), 320–321 (2004).
- 28 Boulman N, Slobodin G, Sharif D, Rozenbaum M, Rosner I: Pseudopodagra: a manifestation of infective endocarditis. *Clin. Exp. Rheumatol.* 23(2), 251–253 (2005).
- 29 Beaudet F, de Medicis R, Magny P, Lussier A: Acute apatite podagra with negative birefringent spherulites in the synovial fluid. *J. Rheumatol.* 20(11), 1975–1978 (1993).
- 30 Chen S, Chen C, Shen M, Kamatani N: Trends in the manifestations of gout in Taiwan. *Rheumatology* 42(12), 1529–1533 (2003).
- 31 Barthelemy I, Karanas Y, Sannajust JP *et al.*: Gout of the temporomandibular joint: pitfalls in diagnosis. *J. Craniomaxillofac. Surg.* 29, 307–310 (2001).
- 32 De Santis D, Palazzi C, D'Amico E *et al.*: Acromioclavicular cyst and “porcupine shoulder” in gout. *Rheumatology* 40, 1320–1321 (2001).
- 33 Currey H: Letter: primary gout affecting the sternoclavicular joint. *Br. Med. J.* 1(6009), 583–584 (1976).
- 34 Perez-Ruiz F, Calabozo M, Alonso-Ruiz A: Gouty arthritis in the manubriosternal joint. *Ann. Rheum. Dis.* 56(9), 571 (1997).
- 35 Kerr R: Radiologic case study. Sacroiliac joint involvement by gout and hyperparathyroidism. *Orthopedics* 11, 187–190 (1988).
- 36 Justiniano ME, Colmegna I, Gimenez CR, Espinoza LR: Tophaceous gout of the symphysis pubis. *Arthritis Rheum.* 52(12), 4052 (2005).
- 37 Parhami N, Feng H: Gout in the hip joint. *Arthritis Rheum.* 36, 1029 (1993).
- 38 Nakajima A, Kato Y, Yamanaka H *et al.*: Spinal tophaceous gout mimicking a spinal tumor. *J. Rheumatol.* 31, 1459–1460 (2004).
- 39 Weinzweig J, Fletcher JW, Linburg RM: Flexor tendinitis and median nerve compression caused by gout in a patient with rheumatoid arthritis. *Plast. Reconstr. Surg.* 106, 1570–1572 (2000).
- 40 Hall A, Barry P, Dawber T, McNamara P: Epidemiology of gout and hyperuricemia: a long-term population study. *Am. J. Med.* 42, 27–37 (1967).
- 41 Campion E, Glynn R, DeLabry L: Asymptomatic hyperuricemia. *Am. J. Med.* 82, 421–426 (1987).
- 42 Wolfe F, Cathey MA: The misdiagnosis of gout and hyperuricemia. *J. Rheumatol.* 18, 1232–1234 (1991).
- 43 Urano W, Yamanaka H, Tsutani H *et al.*: -The inflammatory process in the mechanism of decreased serum uric acid concentration during acute gouty arthritis. *J. Rheumatol.* 29, 1950–1953 (2002).
- **This paper and references [44,45] show that serum urate can be normal during gouty attacks due to raised urate renal clearance. This can be a cause of gout misdiagnosis to be kept in mind.**
- 44 Logan J, Morrison E, McGill P: Serum uric acid in acute gout. *Ann. Rheum. Dis.* 56, 696–697 (1997).
- 45 Schlesinger N, Baker D, Schumacher HR: Serum urate during bouts of acute gouty arthritis. *J. Rheumatol.* 24(11), 2265–2266 (1997).
- 46 Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yu T-F: Preliminary criteria for the classification of the acute arthritis of primary gout. *Arthritis Rheum.* 20, 895–900 (1977).
- 47 Malik A, Schumacher H, Dinnella J, Clayburne G: Clinical diagnostic criteria for gout: comparison with the gold standard of synovial fluid crystal analysis. *J. Clin. Rheumatol.* 15, 22–24 (2007).
- **Demonstrates the poor sensitivity and specificity of Wallace's ACR criteria when compared with diagnosis based in crystal identification.**
- 48 Yu K, Luo S, Liou L *et al.*: Concomitant septic and gouty arthritis – an analysis of 30 cases. *Rheumatology* 42(9), 1062–1066 (2003).
- 49 Suk KS, Kim KT, Lee SH *et al.*: Tophaceous gout of the lumbar spine mimicking pyogenic discitis. *Spine J.* 7, 94–99 (2007).
- 50 Wazir NN, Moorthy V, Amalourde A, Lim HH: Tophaceous gout causing atlanto-axial subluxation mimicking rheumatoid arthritis: a case report. *J. Orthop. Surg. (Hong Kong)* 13(2), 203–206 (2005).
- 51 Li TJ, Lue KH, Lin ZI, Lu KH: Arthroscopic treatment for gouty tophi mimicking an intra-articular synovial tumor of the knee. *Arthroscopy* 22(8), 910, E1–E3 (2006).
- 52 Filippucci E, Riveros MG, Georgescu D, Salaffi F, Grassi W: Hyaline cartilage involvement in patients with gout and calcium pyrophosphate deposition disease. An ultrasound study. *Osteoarthr. Cartil.* 17(2), 178–181 (2009).
- 53 Wright S, Filippucci E, McVeigh C *et al.*: High-resolution ultrasonography of the first metatarsophalangeal joint in gout: a controlled study. *Ann. Rheum. Dis.* 66(7), 859–864 (2007).
- 54 Thiele R, Schlesinger N: Diagnosis of gout by ultrasound. *Rheumatology* 46(7), 1116–1121 (2007).

- 55 Grassi W, Meenagh G, Pascual E, Filippucci E: "Crystal Clear"-sonographic assessment of gout and calcium pyrophosphate deposition disease. *Semin. Arthritis Rheum.* 36(3), 197–202 (2006).
- **This and reference [52] neatly show that urate crystals deposit in the surface of hyaline cartilage, while CPPD crystals deposit in its depths.**
- 56 Rettenbacher T, Ennemoser S, Weirich H *et al.*: Diagnostic imaging of gout: comparison of high-resolution US versus conventional X-ray. *Eur. Radiol.* 18(3), 621–630 (2008).
- 57 Jordan KM, Cameron JS, Snaith M *et al.*: British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (SGAWG) British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology* 46, 1372–1374 (2007).
- 58 Keith MP, Gilliland WR: Updates in the management of gout. *Am. J. Med.* 120, 221–224 (2007).
- 59 Pascual E, Sivera F: Therapeutic advances in gout. *Curr. Opin. Rheumatol.* 19, 122–127 (2007).
- 60 Schlesinger N: Management of acute and chronic gouty arthritis: present state-of-the-art. *Drugs* 64(21), 2399–2416 (2004).
- 61 Yu T-F, Gutman AB. Mobilization of gouty tophi by protracted use of uricosuric agents. *Am. J. Med.* 11, 765–769 (1951).
- 62 Perez-Ruiz F, Liote F: Lowering serum uric acid levels: what is the optimal target for improving clinical outcomes in gout? *Arthritis Rheum.* 57, 1324–1328 (2007).
- 63 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.* 28(3), 577–580 (2001).
- 64 Perez-Ruiz F, Calabozo M, Pijoan JI, Herrero-Beites AM, Ruibal A: Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. *Arthritis Rheum.* 47, 356–360 (2002).
- **Demonstrates that lower serum uric acid levels result in faster reduction of tophi size. This is an important practical observation supporting the aim of maintaining serum uric acid levels as low as possible to achieve a faster elimination of the deposited urate crystals.**
- 65 Baraf HS, Matsumoto AK, Maroli AN, Waltrip RW 2nd: Resolution of gouty tophi after twelve weeks of pegloticase treatment. *Arthritis Rheum.* 58(11), 3632–3634 (2008).
- 66 Puig JG, de Miguel E, Castillo MC, Rocha AL, Martínez MA, Torres RJ: Asymptomatic hyperuricemia: impact of ultrasonography. *Nucleosides Nucleotides Nucleic Acids* 27(6), 592–595 (2008).
- 67 Vukmir RB, Weiss L, Verdile VP: Polyarticular symmetric tophaceous joint inflammation as the initial presentation of gout. *Am. J. Emerg. Med.* 8(1), 43–45 (1990).
- 68 Meyers OL, Monteagudo FSE: Gout in females: an analysis of 92 patients. *Clin. Exp. Rheumatol.* 3, 105–109 (1985).
- 69 Dalbeth N, Clark B, Gregory K *et al.*: Mechanisms of bone erosion in gout; a quantitative analysis using plain radiography and computed tomography. *Ann. Rheum. Dis.* (2008) (Epub ahead of print).
- **Demonstrates that erosions in gout result from intraosseous tophi.**
- 70 Pascual E, Jovani V: A quantitative study of the phagocytosis of urate crystals in the synovial fluid of asymptomatic joints of patients with gout. *Br. J. Rheumatol.* 34, 724–726 (1995).
- 71 Pascual E, Castellano JA: Treatment with colchicine decreases the white cell counts in the synovial fluid of asymptomatic knees which contain monosodium urate crystals. *J. Rheumatol.* 19, 600–603 (1992).
- 72 Krishnan E, Baker JF, Furst DE, Schumacher HR: Gout and the risk of acute myocardial infarction. *Arthritis Rheum.* 54, 2688–2696 (2006).
- **This paper and references [73–75] associate gout to myocardial infarction; among other factors the likely link is the inflammation during attacks and persistence during asymptomatic periods related to the urate crystals. The clinical significance of this association is still under research, but it may indicate that urate crystal deposit – even if asymptomatic – is harmful for the patient and should be eliminated as soon as detected.**
- 73 Choy HK, Curhan G: Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* 116, 894–900 (2007).
- 74 Chen SY, Chen CL, Shen ML: Severity of gouty arthritis is associated with Q-wave myocardial infarction: a large-scale, cross-sectional study. *Clin. Rheumatol.* 26, 308–313 (2007).
- 75 Sattar N, McCarey DW, Capell H, McInnes IB: Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. *Circulation* 108, 2957–2963 (2003).
- 76 Roman MJ, Shanker BA, Davis A *et al.*: Prevalence and correlates of accelerated atherosclerosis in systemic lupus erythematosus. *N. Engl. J. Med.* 349, 2399–2406 (2003).
- 77 Alderman MH: Podagra, uric acid, and cardiovascular disease. *Circulation* 116, 880–883 (2007).
- 78 van Lieshout-Zuidema MF, Breedveld FC: Withdrawal of longterm antihyperuricemic therapy in tophaceous gout. *J. Rheumatol.* 20, 1383–1385 (1993).
- 79 Bull PW, Scott JT: Intermittent control of hyperuricemia in the treatment of gout. *J. Rheumatol.* 16, 1246–1248 (1989).
- 80 Perez-Ruiz F, Atxotegi J, Hernando I, Calabozo M, Nolla JM: Using serum urate levels to determine the period free of gouty symptoms after withdrawal of long-term urate-lowering therapy: a prospective study. *Arthritis Rheum.* 55, 786–790 (2006).
- 81 Richette P, Briere C, Hoenen-Clavert V, Loeuille D, Bardin T: Rasburicase for tophaceous gout not treatable with allopurinol: an exploratory study. *J. Rheumatol.* 34, 2093–2098 (2007).
- **Interesting comparison of two schemes of administration of rasburicase.**
- 82 Day RO, Graham GG, Hicks M, McLachlan AJ, Stocker SL, Williams KM: Clinical pharmacokinetics and pharmacodynamics of allopurinol and oxypurinol. *Clin. Pharmacokinet.* 46, 623–644 (2007).
- 83 Product information: Zylprim, allopurinol. Faro Pharmaceuticals, Bedminster, NJ, USA (PI revised reviewed 2/2000, 2/99).
- 84 Becker MA, Schumacher HR Jr, Wortmann RL *et al.*: Febuxostat, a novel nonpurine selective inhibitor of xanthine oxidase: a twenty-eight-day, multicenter, Phase II, randomized, double-blind, placebo-controlled, dose-response clinical trial examining safety and efficacy in patients with gout. *Arthritis Rheum.* 52, 916–923 (2005).
- **Randomized trials (also references [85,86]) of a novel xantine oxidase inhibitor, febuxostat.**
- 85 Becker MA, Schumacher HR, Wortmann RL *et al.*: Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N. Eng. J. Med.* 353, 2450–2461 (2005).
- 86 Schumacher HR Jr, Becker MA, Wortmann RL *et al.*: Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: A 28-week, Phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum.* 59, 1540–1548 (2008).
- 87 Perez-Ruiz F, Alonso Ruiz A, Calabozo M, Herrero-Beites A, García-Erauskin G, Ruiz-Lucea E: Efficacy of allopurinol and benzbromarone for the control of hyperuricemia. A pathogenic approach to the treatment of primary chronic gout. *Ann. Rheum. Dis.* 57, 545–549 (1998).

- 88 Reinders MK, Haagsma C, Jansen TL *et al.*: A randomised controlled trial on the efficacy and tolerability with dose-escalation of allopurinol 300–600 mg/day versus benzbromarone 100–200 mg/day in patients with gout. *Ann. Rheum. Dis.* (2008) (Epub ahead of print).
- **Demonstrates the increased efficacy achieved in reaching target levels of urate by escalating allopurinol doses up to 600 mg/day.**
- 89 Reinders MK, van Roon EN, Jansen TL *et al.*: Efficacy and tolerability of urate lowering drugs in gout: a randomised controlled trial of benzbromarone versus probenecid after failure of allopurinol. *Ann. Rheum. Dis.* 68(1), 51–56 (2009).
- 90 Sarawate CA, Brewer KK, Yang W *et al.*: Gout medication treatment patterns and adherence to standards of care from a managed care perspective. *Mayo Clin. Proc.* 81, 925–934 (2006).
- 91 Mikuls TR, Curtis JR, Allison JJ, Hicks RW, Saag KG: Medication errors with the use of allopurinol and colchicine: a retrospective study of a national, anonymous internet-accessible error reporting system. *J. Rheumatol.* 33, 562–566 (2006).
- 92 Riedel AA, Nelson M, Joseph-Ridge N, Wallace K, MacDonald P, Becker M: Compliance with allopurinol therapy among managed care enrollees with gout: a retrospective analysis of administrative claims. *J. Rheumatol.* 31, 1575–1581 (2004).
- 93 Annemans L, Spaepen E, Nash C *et al.*: Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000–2005. *Ann. Rheum. Dis.* 67, 960–966 (2008).
- 94 Emmerson BT, Gordon RB, Thomson DB: Plasma oxipurinol concentrations during allopurinol therapy. *Br. J. Rheumatol.* 26, 445–449 (1987).
- 95 Hande KR, Noone RM, Stone WJ: Severe allopurinol toxicity: description and guidelines for prevention in patients with renal insufficiency. *Am. J. Med.* 76, 47–56 (1984).
- 96 Perez-Ruiz F, Hernando I, Villar I, Nolla JM: Correction of allopurinol dosing should be based on clearance of creatinine, but not plasma creatinine levels: another insight to allopurinol-related toxicity. *J. Clin. Rheumatol.* 11, 129–133 (2005).
- 97 Dalbeth N, Kumar S, Stamp L, Gow P: Dose adjustment of allopurinol according to creatinine clearance does not provide adequate control of hyperuricemia in patients with gout. *J. Rheumatol.* 33, 1646–1650 (2006).
- 98 Dalbeth N, Stamp L: Allopurinol dosing in renal impairment: walking the tightrope between adequate urate lowering and adverse events. *Semin. Dial.* 20, 391–395 (2007).
- 99 Vazquez-Mellado J, Morales EM, Pacheco-Tena C, Burgos-Vargas R: Relation between adverse events associated with allopurinol and renal function in patients with gout. *Ann. Rheum. Dis.* 60, 981–983 (2001).
- 100 Siu YP, Leung KT, Tong MK, Kwan TH: Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am. J. Kidney Dis.* 47, 51–59 (2006).
- **This and references [97,100] show the benefits for renal function of reducing uricemia in patients with renal impairment. The clinical implications of this finding are still being weighted.**
- 101 Perez-Ruiz F, Calabozo M, Herrero-Beites AM, García-Erauskin G, Pijoan JI: Improvement of renal function in patients with chronic gout after proper control of hyperuricemia and gouty bouts. *Nephron* 86, 287–291 (2000).
- 102 Gibson T, Rodgers V, Potter C, Simmonds HA: Allopurinol treatment and its effect on renal function in gout: a controlled study. *Ann. Rheum. Dis.* 41, 59–65 (1982).
- 103 Feig DI, Soletsky B, Johnson RJ: Effect of allopurinol on blood pressure of adolescents with newly diagnosed essential hypertension: a randomized trial. *JAMA* 300, 924–932 (2008).
- 104 Gutierrez-Macias A, Lizarralde-Palacios E, Martinez-Odrizola P, Miguel-De la Villa F: Fatal allopurinol hypersensitivity syndrome after treatment of asymptomatic hyperuricaemia. *BMJ* 331, 623–624 (2005).
- 105 Shalom R, Rimbroth S, Rozenman D, Markel A: Allopurinol-induced recurrent DRESS syndrome: pathophysiology and treatment. *Ren. Fail.* 30, 327–329 (2008).
- 106 Halevy S, Ghislain PD, Mockenhaupt M *et al.*; EuroSCAR Study Group: Allopurinol is the most common cause of Stevens–Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J. Am. Acad. Dermatol.* 58, 25–32 (2008).
- 107 Fam AG, Lewtas J, Stein J, Paton TW: Desensitization to allopurinol in patients with gout and cutaneous reactions. *Am. J. Med.* 93, 299–302 (1992).
- 108 Perez-Ruiz F, Calabozo M, García-Erauskin G, Ruibal A, Herrero Beites AM: Renal underexcretion of uric acid is present in patients with apparent high urinary uric acid output. *Arthritis Rheum.* 47, 610–613 (2002).
- 109 Jansen TL, Reinders MK, van Roon EN, Brouwers JR: Benzbromarone withdrawn from the European market: another case of “absence of evidence is evidence of absence”? *Clin. Exp. Rheumatol.* 22, 651 (2004).
- **This and reference [110] suggest that benzbromarone has no more side effects than other drugs used in gout, and the benefits/inconveniences for the patients of its withdrawal may have not been weighted enough.**
- 110 Lee MH, Graham GG, Williams KM, Ray RO: A benefit–risk assessment of benzbromarone in the treatment of gout. Was its withdrawal from the market in the best interest of patients? *Drug Saf.* 31, 643–665 (2008).
- 111 Kumar S, Ng J, Gow P: Benzbromarone therapy in the management of refractory gout. *N. Z. Med. J.* 118(1217), U1533 (2005).
- 112 Perez-Ruiz F, Calabozo M, Fernandez-Lopez MJ *et al.*: Treatment of chronic gout in patients with renal function impairment. An open, randomized, actively controlled study. *J. Clin. Rheumatol.* 5, 49–55 (1999).
- 113 Zürcher RM, Bock HA, Thiel G: Excellent uricosuric efficacy of benzbromarone in cyclosporin-A treated renal transplant patients: a prospective study. *Nephrol. Dial. Transplant.* 9, 549–551 (1994).
- 114 Marcen R, Gallego N, Orofino L *et al.*: Impairment of tubular secretion of urate in renal transplant patients on cyclosporine. *Nephron* 70, 307–313 (1995).
- 115 Perez-Ruiz F, Gomez-Ullate P, Amenabar JJ *et al.*: Long-term efficacy of hyperuricaemia treatment in renal transplant patients *Nephrol. Dial. Transplant.* 18(3), 603–606 (2003).
- 116 Becker MA, Kisicki J, Khosravan R *et al.*: Febuxostat (TMX-67), a novel, non-purine, selective inhibitor of xanthine oxidase, is safe and decreases serum urate in healthy volunteers. *Nucleosides Nucleotides Nucleic Acids* 23, 1111–1116 (2004).
- 117 Mayer MD, Khosravan R, Vernillet L, Wu JT, Joseph-Ridge N, Mulford DJ: Pharmacokinetics and pharmacodynamics of febuxostat, a new non-purine selective inhibitor of xanthine oxidase in subjects with renal impairment. *Am. J. Ther.* 12, 22–34 (2005).
- 118 Watanabe S, Kang DH, Feng L *et al.*: Uric acid, hominoid evolution, and the pathogenesis of salt-sensitivity. *Hypertension* 40(3), 355–360 (2002).
- **Good paper (and [119]) on the mutations that led to inactivation of uricase and resulted in higher urate levels in men and higher primates, and its possible benefits.**
- 119 Oda M, Satta Y, Takenaka O, Tanaka N: Loss of urate oxidase activity in hominoids and its evolutionary implications. *Mol. Biol. Evol.* 19, 240–253 (2002).
- 120 Goldman SC, Holcemberg JS, Finkenshtein JZ *et al.*: A randomized comparison between rasburicase and allopurinol with lymphoma or

- leukemia at high risk for tumor lysis. *Blood* 97, 2998–3003 (2001).
- 121 Vogt B: Urate oxidase (rasburicase) for treatment of severe tophaceous gout. *Nephrol. Dial. Transplant.* 20, 431–433 (2005).
- 122 Richette P, Bardin T: Successful treatment with rasburicase of tophaceous gout in a patient allergic to allopurinol. *Nat. Clin. Pract. Rheumatol.* 2, 338–342 (2006).
- 123 Moolenburgh JD, Reinders MK, Jansen TL: Rasburicase treatment in severe tophaceous gout: a novel therapeutic option. *Clin. Rheumatol.* 25, 749–752 (2006).
- 124 Cammalleri L, Malaguarnera M: Rasburicase represents a new tool for hyperuricemia in tumor lysis syndrome and in gout. *Int. J. Med. Sci.* 4, 83–93 (2007).
- 125 Sundy JS, Becker MA, Baraf HS *et al.*: Reduction of plasma urate levels following treatment with multiple doses of pegloticase (polyethylene glycol-conjugated uricase) in patients with treatment-failure gout: Results of a Phase II randomized study. *Arthritis Rheum.* 58, 2882–2891 (2008).
- 126 Sutaria S, Katbamna R, Underwood M: Effectiveness of interventions for the treatment of acute and prevention of recurrent gout – a systematic review. *Rheumatology* 45, 1422–1431 (2006).
- 127 Rubin BR, Burton R, Navarra S *et al.*: Efficacy and safety profile of treatment with etoricoxib 120 mg once daily compared with indomethacin 50 mg three times daily in acute gout: a randomized controlled trial. *Arthritis Rheum.* 50, 598–606 (2004).
- **Interesting since it is one of the very few randomized control trials comparing two NSIADs for acute gouty arthritis.**
- 128 Janssens HJ, Janssen M, van de Lisdonk EH, van Riel PL, van Weel C: Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. *Lancet* 371(9627), 1854–1860 (2008).
- **Randomized trial showing equivalence of naproxen and prednisone. NSAIDs are often used as drugs of choice for acute gouty inflammation, but glucocorticoids appear a safer choice for elderly patients and those with comorbidities for whom the side effects of NSAIDs are a risk.**
- 129 Groff GD, Franck WA, Raddatz DA: Systemic steroid therapy for acute gout: a clinical trial and review of the literature. *Semin. Arthritis Rheum.* 19, 329–336 (1990).
- 130 Janssens HJEM, Lucassen PLBJ, Van de Laar FA, Janssen M, Van de Lisdonk EH: Systemic corticosteroids for acute gout. *Review Cochrane Syst. Rev.* 16(2), CD005521 (2008).
- 131 Ritter J, Kerr LD, Valeriano-Marcet J, Spiera H: ACTH revisited: effective treatment for acute crystal induced synovitis in patients with multiple medical problems. *J. Rheumatol.* 21, 696–699 (1994).
- 132 Fernandez C, Gonzalez JA, Noguera R, Pascual E: Treatment of acute attacks of gout with a small dose of intraarticular triamcinolone acetonide. *J. Rheumatol.* 26(10), 2285–2286 (1999).
- 133 Pascual E, Trenor P, Medrano C: Management of gout in patients with renal insufficiency and a gastrointestinal bleed – an answer to Dr Dunne’s letter. *Br. J. Rheumatol.* 34, 481–482 (1995).
- 134 Ahern MJ, Reid C, Gordon TP, McCredie M, Brooks MP, Jones M: Does colchicine work? The results of the first controlled study in acute gout. *Aust. N. Z. J. Med.* 17, 301–304 (1987).
- 135 Terkeltaub R, Furst DE, Bennett K, Kook K, Davis M: Low dose (1.8 mg) vs high dose (4.8 mg) oral colchicine regimens in patients with acute gout flare in a large, multicenter, randomized, double-blind, placebo-controlled, parallel group study. *Arthritis Rheum.* 58(Abstract) (2008) (In press).
- **Shows that the effective dose of colchicine for acute gouty arthritis is low and better tolerated than the higher doses often used, which in elderly subjects – or subjects with renal failure – can be very toxic.**
- 136 Terkeltaub RA: Colchicine update: 2008. *Semin. Arthritis Rheum.* (2008) (Epub ahead of print).
- **Very good review on colchicine use, side effects, toxicities and drug interactions.**
- 137 Altman A, Szyper-Kravitz M, Shoenfeld Y: Colchicine-induced rhabdomyolysis. *Clin. Rheumatol.* 26, 2197–2199 (2007).
- 138 Tausche AK, Richter K, Grassler A, Hansel S, Roch B, Schroeder HE: Severe gouty arthritis refractory to anti-inflammatory drugs: treatment with anti-tumour necrosis factor α as a new therapeutic option. *Ann. Rheum. Dis.* 64, 516 (2005).
- 139 So A, De Smedt T, Revaz S, Tschopp J: A pilot study of IL-1 inhibition by anakinra in acute gout. *Arthritis Res. Ther.* 9, R28 (2007).
- 140 Paulus HE, Schlosstein LH, Godfrey RG, Klinenberg JR, Bluestone R: Prophylactic colchicine therapy of intercritical gout. A placebo-controlled study of probenecid-treated patients *Arthritis Rheum.* 17(5), 609–614 (1974).
- 141 Yu T: The efficacy of colchicine prophylaxis in articular gout. A reappraisal after 20 years. *Semin. Arthritis Rheum.* 12, 256–264 (1992).
- 142 Cronstein BN, Molad Y, Reibman J, Balakhane E, Levin RI, Weissmann G: Colchicine alters the quantitative and qualitative display of selectins on endothelial cells and neutrophils. *J. Clin. Invest.* 96(2), 994–1002 (1995).
- 143 Borstad GC, Bryant LR, Abel MP, Scroggie DA, Harris MD, Alloway JA: Colchicine for prophylaxis of acute flares when initiating allopurinol for chronic gouty arthritis. *J. Rheumatol.* 31, 2429–2432 (2004).
- 144 Beutler AM, Rull M, Schlesinger N, Baker DG, Hoffman BI, Schumacher HR Jr: Treatment with allopurinol decreases the number of acute gout attacks despite persistently elevated serum uric acid levels. *Clin. Exp. Rheumatol.* 19, 595 (2001).
- 145 Sarawate CA, Patel PA, Schumacher HR Jr, Yang W, Brewer KK, Bakst AW: Serum urate levels and gout flares: analysis from managed care data. *J. Clin. Rheumatol.* 12, 61–65 (2006).
- 146 Ordi J, Alonso PL, de Zulueta J *et al.*: The severe gout of Holy Roman Emperor Charles V. *N. Engl. J. Med.* 355(5), 516–520 (2006).
- 147 Roddy E, Zhang W, Doherty M: The changing epidemiology of gout. *Nat. Clin. Pract. Rheumatol.* 3(8), 443–449 (2007).
- 148 Miao Z, Li C, Chen Y *et al.*: Dietary and lifestyle changes associated with high prevalence of hyperuricemia and gout in the Shandong coastal cities of Eastern China. *J. Rheumatol.* 35(9), 1859–1864 (2008).
- 149 Choi HK, Ford ES, Li C, Curhan G: Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum.* 57(1), 109–115 (2007).
- 150 Choi HK, Ford ES: Prevalence of the metabolic syndrome in individuals with hyperuricemia. *Am. J. Med.* 120(5), 442–447 (2007).
- 151 Facchini F, Chen Y-D, Hollenbeck CB, Reaven GM: Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA* 266, 3008–3011 (1991).
- 152 Tinahones FJ, Perez Lindon G, C-Soriguer FJ, Pareja A, Sanchez Guijo P, Collantes E: Dietary alterations in plasma very low density lipoprotein levels modify renal excretion of urates in hyperuricemic-hypertriglyceridemic patients. *J. Clin. Endocrinol. Metab.* 82, 1188–1191 (1997).
- **Shows that obese patients with hyperlipemia reduce urate levels by rising urate clearance when switched to a hypocaloric, low-fat diet.**
- 153 Lee SJ, Terkeltaub RA, Kavanaugh A: Recent developments in diet and gout. *Curr. Opin. Rheumatol.* 18, 193–198 (2006).

- 154 Choi HK, Curhan G: Gout: epidemiology and lifestyle choices. *Curr. Opin. Rheumatol.* 17, 341–345 (2005).
- 155 Fam AG: Gout: excess calories, purines, and alcohol intake and beyond. Response to a urate-lowering diet. *J. Rheumatol.* 32, 773–777 (2005).
- 156 Saag KG, Choi H: Epidemiology, risk factors, and lifestyle modifications for gout. *Arthritis Res. Ther.* 8 (Suppl. 1), S2 (2006).
- 157 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.* 59, 109–116 (2008).
- 158 Choi HK, Curhan G: Soft drinks, fructose consumption, and the risk of gout in men: prospective cohort study. *BMJ* 336, 309–312 (2008).
- 159 Choi HK, Willett W, Curhan G: Coffee consumption and risk of incident gout in men: a prospective study. *Arthritis Rheum.* 56(6), 2049–2055 (2007).
- 160 Choi HK, Curhan G: Coffee, tea and caffeine consumption and serum uric acid level: the third national health and nutrition examination survey. *Arthritis Rheum.* 57(5), 816–821 (2007).
- 161 Choi HK, Liu S, Curhan G: Intake of purine-rich foods, protein and dairy products and relationship to serum levels of uric acid; the Third National Health and Nutrition Examination Survey. *Arthritis Rheum.* 52(1), 283–289 (2005).
- 162 Hunter DJ, York M, Chaisson CE, Woods R, Niu J, Zhang Y: Recent diuretic use and the risk of recurrent gout attacks: the online case-crossover gout study. *J. Rheumatol.* 33, 1341–1345 (2006).
- 163 Janssens HJ, van de Lisdonk EH, Janssen M, van den Hoogen HJ, Verbeek AL: Gout, not induced by diuretics? A case-control study from primary care. *Ann. Rheum. Dis.* 65(8), 1080–1083 (2006).
- 164 Pascual E, Perdiguero M: Gout, diuretics and the kidney. *Ann. Rheum. Dis.* 65, 981–982 (2006).
- 165 Scott JT: Drug-induced gout. *Baillieres Clin. Rheumatol.* 5, 39–60 (1991).

■ Websites

- 201 American College of Rheumatology: Core curriculum outline for rheumatology fellowship programs: a competency-based guide to curriculum development (2006). www.rheumatology.org/educ/training/cco.doc
- 202 UEMS Section of Rheumatology: core curriculum for specialist training. www.uems-rheumatology.net/

CME Gout: new advances in the diagnosis and management of an old disease

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
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The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. Which of the following statements about the diagnosis of gout is most accurate?

- A** Gouty arthritis can occur in the absence of monosodium urate crystals
- B** Over 90% of first gouty attacks occur in the first metatarsophalangeal joint
- C** Most patients with a serum uric acid (SUA) level above 9 mg/dl will develop gout within 1 year
- D** The American College of Rheumatology (ACR) clinical criteria lack sensitivity in diagnosing primary gout

2. SUA levels should be reduced to at least which of the following levels to clear crystals from joints?

- A** 10 mg/dl
- B** 8 mg/dl
- C** 6 mg/dl
- D** 4 mg/dl

3. Which of the following statements about the use of medications to reduce SUA levels is most accurate?

- A** Most patients receive adequate reductions in SUA levels with allopurinol 300 mg daily
- B** The dose of allopurinol should be reduced when the creatinine clearance is below 50 ml/min
- C** Febuxostat should be avoided among patients with any degree of renal insufficiency
- D** Allopurinol promotes more side effects than febuxostat

4. Which of the following statements about the treatment of gout-related inflammation is most accurate?

- A** Among nonsteroidal anti-inflammatory drugs (NSAIDs), only indomethacin has been demonstrated to be effective in the treatment of gout-related inflammation
- B** Selective inhibitors of cyclo-oxygenase-2 are not effective in the treatment of gout
- C** Prednisone has been demonstrated to be similarly effective as naproxen in the treatment of gout-related inflammation
- D** Colchicine should only be used in high doses in the treatment of gout-related inflammation