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Gout: a review of its aetiology and treatment

縱評痛風症的病因與醫治方法

Objective. To review the current understanding of the causes and the management of gout.

Data sources. Publications on all peer-review literature from MEDLINE from 1965 to January 2004.

Study selection. Selected and evaluated by the author.

Data extraction. Extracted and evaluated by the author.

Data synthesis. The underlying metabolic disorder in gout is hyperuricaemia. Most patients with hyperuricaemia remain asymptomatic throughout their lifetime. The phase of asymptomatic hyperuricaemia ends with the first attack of gouty arthritis or urolithiasis. The risk of gout and stone formation is increased with the degree and duration of hyperuricaemia. Drugs available for the treatment of acute gouty arthritis, such as non-steroidal anti-inflammatory drugs, selective cyclo-oxygenase 2 inhibitors, systemic corticosteroids, or colchicine, are effective. For periods between attacks, prophylactic therapy, such as low-dose colchicine, is effective. In those with recurrent attacks of more than two to three times yearly, a uric acid–lowering agent as a long-term therapy should be considered to avoid recurrence and the development of tophaceous gout.

Conclusions. Effective management of gout can be achieved through better understanding of the causes of the condition, preventive measures as well as drug treatment.

目的：檢討目前對痛風症成因和醫護方法的認識。

資料來源：以 MEDLINE 系統檢索在 2004 年 1 月前發表的經同業審讀的文獻。

研究選擇：由作者挑選和評估。

資料提取：由作者提取和評估。

資料綜合：高尿酸血症是痛風症代謝紊亂的根本。大部分患有高尿酸血症的病人在生時不會出現任何症狀。病人一旦出現痛風性關節炎或尿石症，即反映無症狀高尿酸血症階段結束，而高尿酸血症愈嚴重、持續時間愈長，痛風和結石的威脅就愈大。能有效治療急性痛風性關節炎的藥物包括非甾體類抗炎藥、選擇性環氧化酶2抑制劑、系統性皮質類固醇以及秋水仙鹼。在病症復發的間歇期，施用少劑量秋水仙鹼類的藥物，是一項有效的預防治療措施。對痛風每年復發兩三次以上的病人，應當考慮施用降尿酸劑作長期治療，防止痛風復發以及形成痛風石關節炎。

結論：進一步了解痛風的成因、預防措施和藥物治療方法，有利於有效處理痛風症。

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Introduction

Gout is a heterogenous group of diseases resulting from the deposition of urate (as monosodium urate monohydrate) crystals in supersaturated extracellular fluids. Clinical manifestations include the following: (1) recurrent attacks of acute gouty arthritis; (2) accumulation of crystalline deposits in periarticular areas, osseous tissues, ligaments, and soft tissue referred to as tophi; (3) uric acid stone formation; (4) and acute uric nephropathy due to a dramatic increase in the plasma urate concentration, thereby causing precipitation of uric acid in the distal tubules and collecting ducts, and resulting in acute tubular necrosis and possible renal failure. The underlying metabolic disorder in gout is hyperuricaemia.

Purine metabolism

In humans, uric acid is derived from ingested foods containing purine and from
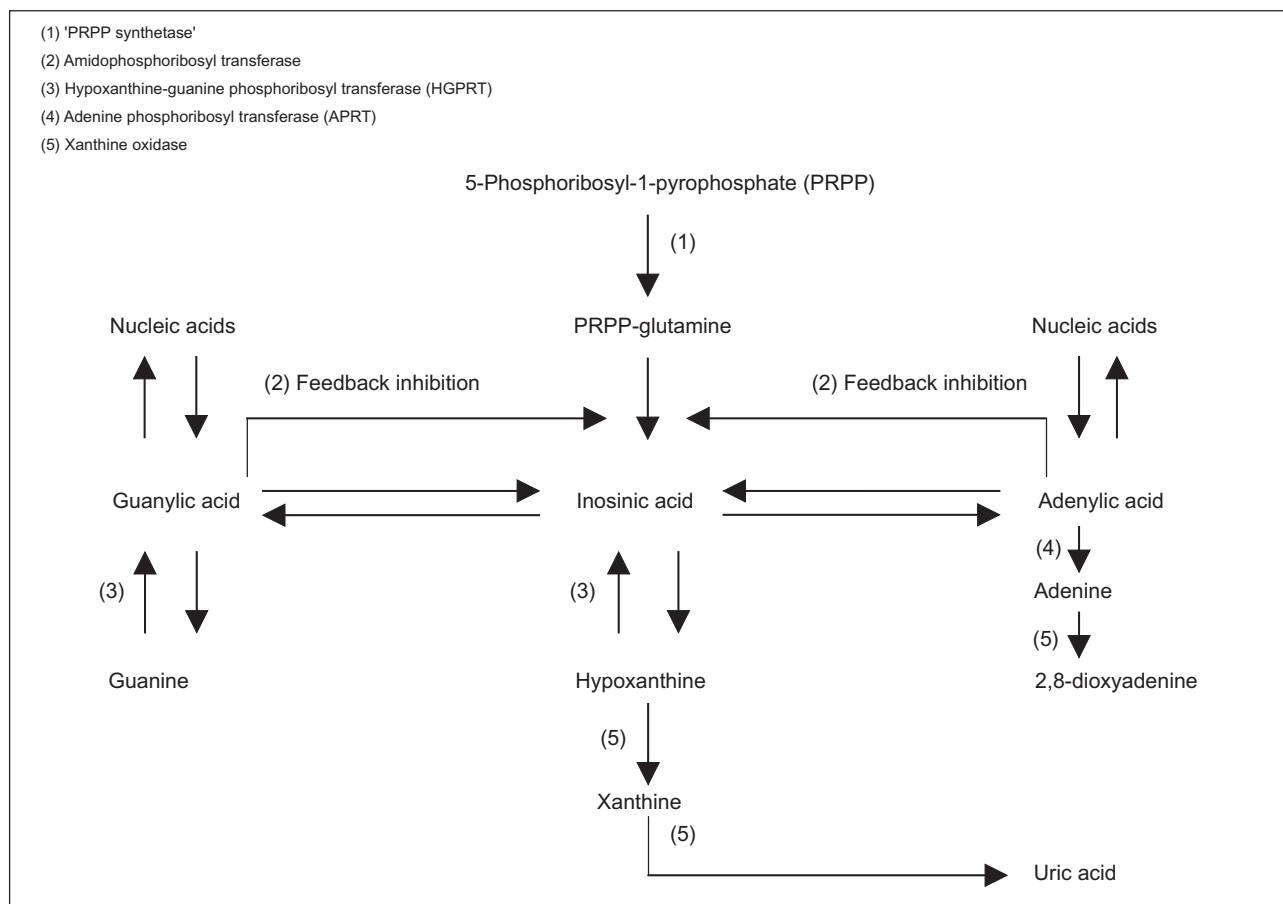
(1) 'PRPP synthetase'

(2) Amidophosphoribosyl transferase

(3) Hypoxanthine-guanine phosphoribosyl transferase (HGPRT)

(4) Adenine phosphoribosyl transferase (APRT)

(5) Xanthine oxidase

5-Phosphoribosyl-1-pyrophosphate (PRPP)

(1)

Nucleic acids   PRPP-glutamine   Nucleic acids

(2) Feedback inhibition   (2) Feedback inhibition

Guanylic acid   Inosinic acid   Adenylic acid

(4) Adenine

(3)   (3)   (5) 2,8-dioxyadenine

Guanine   Hypoxanthine

(5)

Xanthine

(5)   Uric acid

Fig. Outline of purine metabolism

endogenously synthesised purine nucleotides, which are used to form nucleic acid. Urate is a breakdown product of the purine residues of nucleic acids (Fig).

De novo synthesis of purine relies on a key compound, 5-phosphoribosyl-l-pyrophosphate, which is converted enzymatically to inosinic acid, which in turn can either be converted into bases for inclusion into nucleic acids or be broken down into xanthine to form uric acid. Purine nucleotide synthesis can also occur through the activities of two different enzymes, which catalyse the single-step synthesis of a purine nucleotide from a purine base substrate. During the reverse process, the intermediate breakdown product hypoxanthine can be 'salvaged' by the enzyme hypoxanthine-guanine phosphoribosyl transferase and reincorporated into nucleic acid. The whole pathway is tightly regulated and is controlled by feedback inhibition. The breakdown products of purine nucleotides eventually become xanthine, which is then oxidised to uric acid.

Uric acid is a weak acid with pKa, 5.75-10.3. At the physiological pH of 7.4, some 99% of the compound is in the ionised form of urate—in the blood mostly as monosodium urate, and in the urine as potassium, ammonium, and calcium urates. Only in the parts of the urinary tract where the pH is less than 5.7 are most of the molecules in the form of uric acid.

Hyperuricaemia

Hyperuricaemia is defined as a serum urate concentration that exceeds the saturation value of urate in the plasma at 37°C—a value representing supersaturation in a physiochemical sense. The upper limit of the normal range of urate levels is 0.416 mmol/L (7 mg/dL) in men and 0.357 mmol/L (6 mg/dL) in women. The serum urate concentration varies with the age and sex of the person. Children normally have a lower concentration, in the range of 0.177 to 0.240 mmol/L, because of high renal uric acid clearance.[1] At puberty, in men, the serum urate level increases by 0.150 to 0.600 mmol/L, this level is generally sustained throughout life. In contrast, in women urate levels remain constant until after menopause, when they begin to rise to approach the values seen for adult men.[2] The lower value in women is because of oestrogen, which promotes excretion of urate during the childbearing period.[3]

Hyperuricaemia can be due to increased urate production, decreased excretion, or both (Table 1). Alcohol may both increase the production of uric acid and impair its excretion. In western countries, almost 10% of adults have hyperuricaemia at least once during their lifetime. In a hospitalised population, 13.2% of all adult men exhibited hyperuricaemia.[4] In Britain, the prevalence of gout was

Table 1. Causes of hyperuricaemia[9]

Increased urate production	Reduced urate excretion
Primary hyperuricaemia	Primary (idiopathic) hyperuricaemia
Phosphoribosyl pyrophosphate synthetase overactivity	
Hypoxanthine-guanine phosphoribosyl transferase deficiency	
Secondary hyperuricaemia	Secondary hyperuricaemia
Excessive dietary purine intake	Decreased renal function
High nucleotide turnover (psoriasis, myeloproliferative, lymphoproliferative diseases)	Inhibition of urate secretion (ketoacidosis, lactic acidosis)
Increased adenosine triphosphate degradation (vigorous muscle exertion)	Unknown mechanism
	Hypertension
	Drugs (low-dose salicylate, diuretics, pyrazinamide, ethambutol, warfarin, cyclosporine, theophylline, levodopa, nicotinic acid, alcohol)
	Lead nephropathy

Table 2. Incidence of gout in relation to serum uric acid level[9,31]

Serum urate concentration (mmol/L)	Annual incidence of gout (%)	5-year cumulative incidence (%)
<0.416	0.1-0.5	0.6
0.416-0.539	0.5-1.2	4.1
≥0.540	4.9-5.7	19.8

1.0%,[5] whereas in two American studies, 0.7% and 0.5% of middle-aged and older men, respectively, had gout diagnosed, and 0.1% and 0.3% of middle-aged and older women, respectively.[6,7] Filipinos living in the United States had higher rates of gout and hyperuricaemia than did Filipinos in Philippines.[8] In New Zealand, the prevalence of gout among Maoris was 8%, whereas among whites, it was only 0.5%. In Shanghai, the prevalence rate is 0.33%.[9] One study in Taiwan showed that the prevalence of gout in a rural population at 0.16%, was lower than that in an urban population with a prevalence of 0.67%.[10] These data suggest that genetic and environmental factors play pivotal roles in the aetiology of gout.

Although the risk of gout increases with the degree and duration of hyperuricaemia, gout is not common.[11] Among patients with a serum urate concentration of 0.540 mmol/L, the incidence of acute gout is only about 5% per year.[12] And among patients with a serum urate level between 0.416 and 0.539 mmol/L who were followed for 14 years, gout developed only in 12% (Table 2).[13]

The prevalence of renal stones in adults in the United States is estimated to be 0.01%.[3] However, uric acid stones occur in about 20% of patients with gout. The risk of developing renal calculi in asymptomatic hyperuricaemia is 0.3%, and in patients with gout the risk is 3 times higher at 0.9%.[14]

Acute uric acid nephropathy develops after a dramatic increase in serum urate production, such as that occurring in acute tumour lysis syndrome among patients undergoing chemotherapy for lymphoproliferative or myeloproliferat-

ive diseases. It can also occur following the introduction of potent uricosuric therapy if the urine is not alkalinised and is concentrated. This preventable and reversible cause of acute renal insufficiency is due to precipitation of uric acid in the renal tubules and collecting ducts, which obstructs urinary flow.

Some researchers consider hyperuricaemia as a risk factor for ischaemic heart diseases, but the data so far do not prove this.[15] The lack of evidence is in part because of the difficulty in proving a direct association in a disease in which confounders such as hypertension, diabetes mellitus, and drug treatments coexist.[13] Similarly, the link between hyperuricaemia, dyslipidaemia, and metabolic syndrome X is also controversial.

Most patients with hyperuricaemia remain asymptomatic throughout their lives. When the serum urate concentration is elevated, the risk of developing acute gouty arthritis and urolithiasis increases—in most cases, after at least 20 years of sustained hyperuricaemia. The phase of asymptomatic hyperuricaemia ends with the first attack of gouty arthritis or urolithiasis. Asymptomatic hyperuricaemia alone has not been linked to the development of renal disease in large cohorts.[16] Nonetheless, a high serum urate level should prompt the physician to look for a possible correctable cause, such as intermittent alcohol misuse, use of certain drug treatments, underlying metabolic conditions, or malignancy. Because hyperuricaemia itself is not a disease, treatment should be restricted to specific circumstances, such as recurrent attacks of gouty arthritis, topus formation, history of renal calculi, and undergoing chemotherapy.[13]

Acute gouty arthritis

Acute gouty arthritis is predominantly a condition that occurs in men older than 40 years of age. In women, the onset is usually 20 years later. When gout occurs before age 25 or in premenopausal women, specific enzyme defects that cause overproduction of purine needs to be considered. Most acute attacks of gout involve a single joint in the lower limb, most commonly the first metatarsophalangeal joint.

The onset is acute, with a marked increase in pain within hours. Patients often experience difficulty in walking or weight-bearing, and they may become febrile. Acute monoarthritis is seen in 85% of first attacks and often involve the lower limb (eg the first metatarsophalangeal joint of the great toe, the instep, ankle, heel, knee, wrist, fingers, and elbow joints). An attack of gout at axial sites, such as the spine, is rare. Some patients may complain of having a sprained ankle, sore heel, or twinges of pain in the great toe before their first dramatic gouty attack.[16] Often, no specific exacerbating event is noted, but surgery—typically during postoperative days 3 to 5—or acute medical illness, such as infections, can precipitate an attack. Because of these features, gout is sometimes misdiagnosed as septic arthritis or cellulitis.

In women, the onset of gout is usually postmenopausal. Furthermore, atypical presentation of gout is more common in elderly women than in men. The prevalence of gout in women older than 60 years is the same as that in men, and the prevalence is even higher than in men among women older than 80 years.[17] Polyarticular acute gouty attacks are more common. The presentation may have an insidious onset and involve the small joints of the hands either symmetrically or asymmetrically.[18] Tophi are particularly common in previously damaged joints, such as Heberden's nodes. Associated conditions are much more common in elderly women with gout than in men with gout. Diuretic use, hypertension, renal insufficiency, and osteoarthritis have a strong association with the development of postmenopausal gout.[19]

On examination, the affected joint is dusky red, swollen, and extremely tender. Systemic features of inflammation may include leukocytosis and elevation of the erythrocyte sedimentation rate. About 40% of patients with acute gout have a normal serum uric acid level during the attack, possibly as a result of pro-inflammatory cytokines.[20] Radiographs show only soft tissue swelling during the early attacks. The definitive diagnosis is established by aspiration of the joint and identification of intracellular needle-shaped crystals that are negatively birefringent under compensated polarised light microscopy.

The most important risk factor for the development of gout is hyperuricaemia. Other risk factors are male gender, obesity, alcohol use, occupational and environmental lead exposure, hypertension, thiazide diuretic use, renal insufficiency, and family history of gout. These factors are thought to cause acute gouty arthritis by raising the plasma and synovial uric acid concentration to beyond saturation, or by altering the local condition in the joint to favour crystallisation of uric acid.[21]

Chronic tophaceous gout

After 10 years or more of recurrent acute gouty attacks, the patient enters a phase of chronic polyarticular gout during

Table 3. Treatment options in acute gouty arthritis[12]

Drug	Regimen
Indomethacin	150-200 mg/d for 3 days in 3-4 divided doses, then 100 mg/d for 4-7 days in 4 divided doses
Etoricoxib	120 mg for 5 days
Prednisolone	40 mg/d for 3 days, then taper by 10 mg/d for 3-4 days
Triamcinolone acetonide	40 mg for large joints (knees)
Colchicine	0.6 mg/h for 3 hrs, then 0.6 mg twice a day for 1 day

which the intercritical periods are no longer free of pain. The involved joints are persistently painful and are swollen. On examination, there is diffuse symmetric involvement of the small joints in the hands and feet, and tophi that may not be visible in about half of these patients. However, by using magnetic resonance imaging, one can detect periarticular tophi.[22] Chronic tophaceous gout can occasionally be confused with symmetrical polyarthritis or rheumatoid arthritis. Tophi can occur in the helix of ear, the olecronon, finger pads, Achilles tendon, and pressure points such as the ulnar aspect of the forearm. Radiography typically reveals erosions with sclerotic margins, overhanging calcified edges, and punctate-to-diffuse calcification. Joint-space narrowing is minimal despite the large erosions. These changes may sometimes be difficult to distinguish from rheumatoid erosion. Since the introduction of allopurinol and uricosuric drugs, the incidence of tophaceous gout has declined.

Treatment of acute gouty arthritis

Four drugs are effective against acute gouty arthritis (Table 3): non-steroidal anti-inflammatory drugs (NSAIDs), selective cyclo-oxygenase 2 (COX-2) inhibitors, corticosteroids, and colchicine.

Non-steroidal anti-inflammatory drugs
Indomethacin provides pain relief within 2 to 4 hours, particularly if it is taken soon after the acute onset of the attack.[23] Although this drug is widely used, its efficacy is based on only a few studies.[24-27] Only three double-blind studies comparing indomethacin with flurbiprofen,[25] ketoprofen,[24] and proquazone[26] have shown no significant differences in efficacy. Non-comparative studies suggest other NSAIDs, such as piroxicam,[28] ibuprofen,[29] and sulindac[30] are as effective as, but are not better than, indomethacin. The appropriate dosage of indomethacin ranges from 150 to 200 mg/d in three to four divided doses for 3 days, then 100 mg/d for 4 to 7 days as the attack subsides.[31] The usefulness of NSAIDs is limited by their side-effects, especially in elderly patients and those with renal insufficiency.[11]

Non-steroidal anti-inflammatory drugs exert their anti-inflammatory effects mainly by inhibiting the enzyme cyclo-oxygenase, which catalyses the conversion of

arachidonic acid to pro-inflammatory prostagladins, particularly prostaglandin E_2. These prostaglandins have a major role in both experimental and clinical crystal-induced inflammation, and they act synergistically with other mediators, such as bradykinin and leukotriene B_4 to enhance capillary dilatation and neutrophil chemotaxis.[32]

Selective cyclo-oxygenase 2 inhibitors
The only study of the use of COX-2 inhibitors to treat acute gout is a head-to-head comparison between etoricoxib and indomethacin. Etoricoxib 120 mg given once daily to 75 patients with acute gouty attacks was as efficacious as indomethacin 50 mg given 3 times daily for 5 days to another 75 patients.[33]

Corticosteroids
Different preparations of corticosteroid have been shown to be useful in the treatment of acute gouty attacks, including intra-articular injection.[34] Methylprednisolone acetate 5 to 10 mg for small joints and 20 to 60 mg for larger joints such as the knees has been suggested.[11] Other routes of corticosteroid delivery, such as intramuscularly or intravenously, have not been shown to be more efficacious than intra-articular injection. Intravenous methylprednisolone 125 mg/d (n=7), intramuscular betamethasone 7 mg/d (n=10) and oral diclofenac 150 mg/d (n=10) showed no differences in efficacy in a non-randomised, non-blinded study of 27 patients.[35] In addition, intramuscular delivery of corticosteroid (triamcinolone 60 mg/d) was not more effective than oral indomethacin (50 mg 3 times daily). Resolution of symptoms occurred within an average of 7 days for triamcinolone and 8 days for indomethacin.[36] Similarly, intramuscular adrenocorticotrophic hormone (ACTH) 40 IU is as effective as oral indomethacin 50 mg 4 times daily and has a shorter interval to pain relief.[27] In a separate study comparing the effect of ACTH 40 IU compared with intramuscular triamcinolone (60 mg), the time to resolution of symptoms was very similar, suggesting both agents are equally effective despite the higher re-injection rate in those who received ACTH.[37] Oral corticosteroid, such as prednisolone, is equally effective in the treatment of acute gouty attacks.

Colchicine
Although colchicine has been used for centuries for the treatment of acute gout, there is only one published controlled trial of the use of this drug for acute gout. Two thirds of colchicine-treated patients showed improvements in their condition after 48 hours, and all developed diarrhoea after a median of 24 hours. The side-effects occurred before relief of pain for most patients.[38] No blinded controlled study comparing NSAID therapy and colchicine for acute gout has ever been published. The dose of colchicine as recommended by the British National Formulary is 1 mg initially followed by 0.5 mg every 2 to 3 hours until relief of pain is achieved or vomiting or diarrhoea occur, or until a total dose of 6 mg has been reached.[39] Because of the great discomfort for patients and the long duration before pain relief, oral colchicine should not be recommended as a primary treatment, especially in elderly patients.[17,31] Colchicine given intravenously can cause bone marrow suppression and other serious renal, hepatic, and central nervous system injury, and even death. Hence, this preparation is not available locally. In countries such as Great Britain along with many hospitals in the United States have removed parenteral colchicine.[11]

Colchicine interferes with the functions of neutrophils, which have a central role in the inflammatory response. Tubulin-colchicine dimers cap the assembly end of microtubules, thereby interfering with the cell structure and movement and decreasing motility, chemotaxis, release of chemotactic factors, formation of digestive vacuoles, and lysosomal degranulation. It can also inhibit tyrosine phosphorylation and the generation of leukotriene B_4.[11]

Non-pharmacological treatment
In a small, randomised trial of 19 patients, ice therapy on the inflamed joints for 30 minutes, 4 times daily along with drug treatment caused a significant reduction in pain as well as joint circumference as compared with a control group of 9 patients who were given the same drug regimen but without the ice therapy.[40]

Table 4. Prophylaxis for recurrence of gouty arthritis

	Drug	Regimen
Either	Colchicine*	0.5 mg twice a day for patients with normal renal function
		0.5 mg/d creatinine clearance of 35-49 mL/min
		0.5 mg every 2-3 days (creatinine clearance of 10-34 mL/min)
or	Indomethacin plus	25 mg twice a day
	Allopurinol†	300 mg/d with normal creatinine clearance
		200 mg/d with creatinine clearance 40-60 mL/min
		100 mg/d with creatinine clearance 20-40 mL/min
		100 mg every other day with creatinine clearance 10 mL/min
		100 mg every third day with creatinine clearance <10 mL/min
or	Probenecid	2 g/d

* To start after acute attack has subsided for at least 1 week and to be continued for 1 year after serum urate level has normalised
† To start only after colchicines therapy has begun for at least 1 week and to be continued as a long-term therapy

Prophylaxis against acute gout

Pharmacological therapy

Long-term prophylaxis is indicated if attacks occur more than 2 to 3 times a year.[11] Oral low-dose colchicine 0.5 mg twice daily is effective in reducing the frequency of recurrent attack (Table 4). Suppression of chemotactic factor release by synovial lining cells appears to underlie the prophylactic action of colchicine.[41] In a study of 540 patients, low-dose colchicine was effective in 82% of patients, satisfactory in 12%, and ineffective in only 6%.[42] However, in elderly patients, loose bowel movement or diarrhoea may preclude the recommended dose. In patients with reduced creatinine clearance of less than 50 mL/min, colchicine should be given once daily. In those with a clearance of 10 to 34 mL/min, 0.5 mg colchicine every 2 to 3 days is recommended. Colchicine should be avoided in patients with a clearance of less than 10 mL/min and in patients who are receiving haemodialysis or who have underlying hepatic dysfunction.[31] Although the duration of prophylaxis has not been established, therapy should be continued for at least 1 year after the serum urate level has normalised[11] and thereafter, until 6 attack-free months have passed. In patients with tophi, colchicine will need to be continued until these lesions resolve.

In patients who are unable to tolerate colchicine, indomethacin at a dose of 25 mg twice daily is also useful, although data supporting the use of NSAIDs for prophylaxis against gout are sparse.[43] Colchicine neuromyopathy[44] and NSAID-induced stomach ulceration are potential complications of the long-term administration of these agents.

The aim of hypo-uricaemic therapy is to maintain a serum urate concentration of below 0.420 mmol/L—a level substantially below monosodium urate saturation in extracellular fluid. The risk of attacks during the first 6 months was found to be lowest when serum urate was reduced in the range of 0.297 to 0.357 mmol/L (with a 30% reduction in recurrence), compared with the recurrence rates in patients whose serum urate levels remained above this range.[45]

There are two classes of drugs other than using low-dose colchicine available for prophylaxis against acute gout: (1) Uricosuric drugs such as probenecid, sulfinpyrazone, and benzbromarone; and (2) xanthine oxidase inhibitors such as allopurinol.

Antihyperuricaemic therapy
Uricosuric drugs

In general, xanthine oxidase inhibitors are indicated in patients with increased urate production, whereas uricosuric agents are indicated in 'underexcretors' of urates, commonly defined as patients excreting less than 800 mg of uric acid while on a normal diet—that is, they have a defect in their renal handling of uric acid, as evidenced by a lower-than-normal ratio of uric acid clearance to glomerular filtration. The majority of patients with gout are underexcretors, and uricosuric drugs would seem to be a logical choice of therapy. The main problem of using these agents is the promotion of stone formation, because of the increase in the urinary excretion of urate soon after the initiation of therapy. With adequate hydration (eg with 2 L of fluid taken 3 to 4 times daily, preferably alkaline by adding 1 g of sodium carbonate), this complication can be prevented. Satisfactory control of hyperuricaemia can be achieved in 60% of patients receiving probenecid 1 g/d and in 85% of patients receiving 2 g/d. In practice, the long-term control of hyperuricaemia is not adequate in up to 25% of patients.[11] In addition, both uricosuric drugs (probenecid and sulfinpyrazone) are not effective in patients with impaired renal function. Benzbromarone is useful in patients with renal insufficiency, although fulminant hepatic failure has been linked to its use in Japan.[46]

Xanthine oxidase inhibitors

Allopurinol is effective in lowering the serum urate concentration in patients who overproduce or underexcrete urate (or both) and therefore is arguably the easier drug to use than the uricosuric drugs. Throughout the world, clinicians use allopurinol much more frequently than they do other hypouricaemic therapies, irrespective of the cause of hyperuricaemia.[35]

The potential complication of xanthine oxidase inhibitors is the precipitation of acute attacks of gout, especially if colchicine prophylaxis has been omitted. Because any sudden increase or decrease in the serum uric acid concentration can trigger an acute gouty attack, allopurinol therapy should not be started during an acute attack of gout. Although the mechanism for the acute precipitation of acute gout is uncertain, one potential explanation is that neutrophils may be rendered more efficient in phagocytosing urate crystals when urate concentrations are lowered than during the hyperuricaemic state.

The effective dosage of allopurinol is 300 mg/d as a single morning dose in patients with a normal creatinine clearance. This regimen can reduce serum urate concentrations to normal values in 85% of patients with gout.[47] In those with a reduced creatinine clearance (41-60 mL/min), 200 mg/d should be given. Further dosage reduction is required in those with a creatinine clearance of below 20 to 40 mL/min, 100 mg is recommended. Further reduction of the drug to 50 mg/d is required in patients whose renal function is further impaired.[31] Serum urate levels begin to fall within 2 days of therapy and they reach stable levels within 1 to 2 weeks. Although allopurinol is considered to be a safe drug, 2% of patients and 20% of those receiving both allopurinol and penicillin develop rashes.[11] After the drug is discontinued, the rash will usually subside and may not recur if therapy is resumed with a lower dose.

The most serious reaction is allopurinol hypersensitivity syndrome (AHS). Cases often exhibits fever in the range of 39.0℃ to 39.5℃, skin rash which is usually of the maculopapular variety but can become a diffuse erythroderma with exfoliation, toxic epidermal necrolysis or Stevens-Johnson syndrome. Patients may have eosinophilia, hepatitis, and renal failure. Allopurinol hypersensitivity syndrome occurs typically in patients with renal insufficiency who are taking diuretics in addition to a standard dose of allopurinol.[48] It occurs with a frequency of 0.4% and mortality rate approaching 25%.[49] Causes of death include renal and hepatic failure, gastro-intestinal bleeding, and sepsis associated with skin exfoliation. The mean duration from the start of therapy to the onset of symptoms is 3 weeks. More than half of patients in whom this life-threatening reaction develops have no clear indication for allopurinol treatment.[14] To reduce the risk of AHS, the dosage of the drug should be adjusted according to the rate of creatinine clearance.[48] Corticosteroid seems to be effective in such patients but its use in this setting remains controversial.[50] Approximately half of patients with minor hypersensitivity rashes could be successfully desensitised by treatment starting with 10 to 25 μg/d of the drug diluted in oral liquid suspension and gradually doubling the dose every 3 to 14 days until the desired dose is reached.[51]

Allopurinol is also associated with important drug interactions, which include azathioprine, which is metabolised in part by xanthine oxidase. In the treatment of gout in post-transplant recipients, the dosage of azathioprine needs to be reduced by at least 50% to prevent bone marrow suppression. Bone marrow suppression can occur in patients receiving alkylating agents, such as cyclophosphamide, through the increased half-life of allopurinol.[52]

Other drugs
The angiotensin II receptor antagonist losartan has a modest uricosuric effect, which appears to plateau at a dosage of 50 mg/d.[53] The effect is transient and is relatively modest; however, the drug's effect on clinical gout are unknown.[54]

Uricase is an investigational drug that derives its efficacy from the conversion of uric acid to allantoin. Uricase acts on free uric acid and causes the dramatic reduction of uric acid levels in a few hours. Hence, it has been studied in tumour lysis syndrome. Because humans do not make urate oxidase, this enzyme is highly antigenic, and administration of native uricase often results in allergic reactions. Recombinant uricase preparations have recently been used to decrease the immunogenicity of the recombinant protein.[55] Further studies are needed to address this issue.

Diet management
A purine-restricted diet may reduce the mean serum urate concentration by only 0.060 mmol/L and is thus moderately effective. This form of diet is often unpalatable and is not effective in the management of hyperuricaemia. With the availability of antihyperuricaemic drugs, the dietary approach has rarely been used. A small, non-randomised 4-month study of 13 men with a restricted carbohydrate intake and increased protein intake showed an increased incidence in insulin sensitivity despite a constant purine intake. There was an 18% reduction in serum urate level of 0.100 mmol/L and a 67% reduction in the occurrence of gouty attacks, as well as a decline in body weight by a mean of 7.7 kg. Other reversible factors contribute to an increased serum urate level and the increased risk of gout among patients with hyperuricaemia; these factors include alcohol intake, diuretics, and excess weight gain.[56] This finding suggests that dietary and lifestyle modifications may be useful without the use of antihyperuricaemic agents.

Management of hyperuricaemia and gout in special circumstances

Patients with heart failure
The risk of gout in thiazide-treated patients is very small. In the Hypertension Detection and Follow-up Program, there were only 15 episodes of gout in 5 years among 3693 participants.[57] However, all diuretic drugs can cause urate retention with acute gout, more so with loop diuretics than with thiazides.[58] In patients taking a thiazide and no other diuretics, the increased incidence of gout attacks was associated with obesity and high alcohol intake.[59] These risk factors should thus be corrected rather than drug therapy stopped. Hence, for patients with heart failure who are taking diuretics, drug dosages will need reviewing to see if lower doses can be used rather than abruptly stopping all diuretics. Low-dose diuretic therapy of thiazide of less than 25 mg/d and a low-dose loop diuretic of 5 mg of torasemide in hypertensive patients does not seem to alter serum urate levels significantly,[60] and the dose may not be sufficient for those with heart failure.

For those with acute gouty arthritis, NSAIDs may cause sodium and volume retention, especially when used in large doses and if they have a long plasma half-life. Other alternatives, such as colchicine, can be used, but dosages need to be reduced for patients with renal or hepatic insufficiency, and for those who are elderly. Intra-articular injections of glucocorticoids are very useful when the administration of NSAIDs and colchicine is problematic. Oral corticosteroids can worsen heart failure by inducing fluid retention through mineralocorticoid effects.[58] Analgesics, such as paracetamol, can be used as adjunct therapy. Additionally, opioid anagelsics may be used to relieve moderate-to-severe pain.[58]

Patients with chronic renal failure
Gouty arthritis is rare in end-stage renal failure and is related to monocyte-associated immunosuppression and a subsequent reduction in secretion of pro-inflammatory cytokines in response to stimuli such as monosodium urate

crystals. Monocytes in patients with end-stage renal failure produce lower amounts of interleukin (IL)-1β, IL-6, and tumour necrosis factor α than monocytes from healthy patients.[61] In acute attacks, the dose of colchicine needs to be reduced and the drug is to be avoided when the creatinine clearance is below 10 mL/min or in patients undergoing haemodialysis[31]; similarly, NSAIDs are contraindicated. Intra-articular injections of glucocorticoids and systemic corticosteroid are useful. Proper control of hyperuricaemia is important to prevent recurrences. Furthermore, the dose of allopurinol has to be reduced. The reduction of serum uric acid is greater with benzomarone than with allopurinol treatment.[62]

Post-transplant patients using cyclosporin

Gout is common among transplant patients who are exposed to cyclosporin, which reduces renal clearance of uric acid. Concomitant renal function compromise or diuretic therapy also contribute to hyperuricaemia in these patients. The likelihood of developing gout within 8 years after cardiac transplantation is 31%.[63] For these reasons, lower doses of cyclosporine and the avoidance of diuretics is recommended. Azathioprine is metabolised by xanthine oxidase, which is inhibited by allopurinol. As a result, the metabolism of azathioprine is slowed and may result in increased risk of bone marrow toxicity. If azathioprine and allopurinol are used together, to avoid the risk of inadequate immunosuppression with resultant graft rejection on one hand and azathioprine toxicity on the other, they can be started at 25 mg/d and 50 mg/d, respectively.[64] In addition, the complete blood count and serum urate concentration need to be determined, and the dose of allopurinol dose needs to be adjusted to bring the serum urate concentration to less than 0.38 mmol/L.[64]

Benziodarone at a mean dose of more than 75 mg/d was recently shown to be more effective than allopurinol in controlling hyperuricaemia during renal transplantation; the drug also reduced the risk of azathioprine-allopurinol interactions.[65] In acute attacks following renal transplantation, colchicine and NSAIDs may be inappropriate because of their potential toxicities. In patients who are already taking oral corticosteroids, the administration of ACTH or intra-articular steroid injection may not be totally effective, the use of pain medication may become necessary.

Elderly patients

Therapeutic options are essentially the same as listed in Table 3. Many geriatric patients may have underlying renal, cardiac, or hepatic dysfunction, which preclude the use of NSAIDs. In patients experiencing a monoarticular attack, the safest therapeutic option is an intra-articular injection of corticosteroid. In polyarticular disease, oral corticosteroid, such as prednisolone 30 mg/d, is recommended, which should be tapered for 1 to 2 weeks until synovitis resolves.[66] Low-dose colchicine have been advocated for acute gout in elderly patients and in those with renal insufficiency—0.5 mg 3 times a day has been documented

as being effective and having a low likelihood of producing side-effects.[39]

Patients with nephrolithiasis

When hyperuricaemia leads to hyperuricosuria, uric acid stones or calcium stones may form. In addition to identifying the composition of the stone, physicians should ensure that patients increase their fluid intake to produce a daily urine volume of more than 2 L. For those with uric acid stones, urine should be alkalinised to pH 6.0 to 6.5 with sodium bicarbonate or acetazolamide, because uric acid is converted to the more soluble urate form at a higher pH. Allopurinol is the drug of choice in the treatment of nephrolithiasis. It reduces both the plasma and the urinary uric acid concentration. It can also reduce the rate of recurrence of calcium oxalate stones in both gouty and non-gouty patients with hyperuricaemia or hyperuricalciuria.

Patients with acute uric acid nephropathy

Acute uric acid nephropathy is characterised by acute oliguric or anuric renal failure because of uric acid precipitation within the tubules. The condition is most often caused by overproduction and overexcretion of uric acid in patients with lymphoma, leukaemia, or myeloproliferative disease after induction of rapid cell lysis by chemotherapy or radiation.

The diagnosis should be suspected when acute renal failure develops in any of the above settings in association with marked hyperuricaemia (plasma uric acid concentration generally more than 0.89 mmol/L. This diagnosis is different from those of most other forms of acute renal failure in which the plasma uric acid concentration is less than 0.71 mmol/L. The urinalysis may show many uric acid crystals but can also be relatively normal because of the lack of output from the obstructed nephrons.

Prevention is the best therapy. Patients about to receive chemotherapy should be pretreated with allopurinol (in higher than normal doses of 600-900 mg/d) plus fluid loading to maintain a high urine output (>2.5 L/d). In some patients, the degree of cell lysis is so great that even optimal prophylaxis is not completely protective. Haemodialysis to remove the excess circulating uric acid should be started in patients in whom diuresis cannot be induced. A possible alternative approach to prevention or treatment involves degradation of uric acid by the administration of uricase.

Summary

Asymptomatic hyperuricaemia does not require treatment apart from identifying a possible correctable cause, such as alcohol misuse or certain drug treatments, an underlying metabolic condition, or malignancy. Factors that can commonly lead to hyperuricaemia are obesity, regular alcohol consumption, diuretic therapy, and a high-purine diet, and these factors should be identified so that possible correc-

tions can be implemented. Acute gouty arthritis can best be treated with NSAIDs, selective COX-2 inhibitors, or corticosteroid. Colchicine is effective but has unpleasant side-effects and is slow in onset of action. It is generally now unwarranted as a primary treatment. Recurrent gouty attacks of a frequency of more than 2 to 3 times a year should prompt physicians to consider long-term therapy consisting of low-dose colchicine as a prophylactic drug against further attacks, as well as the use of uric acid–lowering agents, such as allopurinol. In patients with renal insufficiency, particular caution is required when these drugs are administered to avoid drug toxicity.

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