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Pathophysiology, Clinical Presentation and Treatment of Gout

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Abstract

Gout is a common form of inflammatory arthritis that has been managed primarily in general medical practices for centuries. It appears that there has been an increasing prevalence of gout over the past decades, implying a growing public

health burden. Accurate diagnosis and recognition of the various stages and manifestations of gout enable realistic goal setting for management. Recent evidence suggests new risk factors and potentially refutes others. Management of gout requires characterising and modifying risk factors and associated disorders, and commonly initiating drug therapy. Pharmacotherapy of gout includes the management of acute flares with anti-inflammatory agents such as NSAIDs and glucocorticoids and long-term treatment with urate-lowering drugs. Although pharmacotherapy is generally safe and effective, there are caveats and limitations to all gout therapies. Patient non-adherence and errors with the use of drugs for gout treatment are important factors leading to medical failures. With early intervention, careful monitoring and patient education, gout is a condition that can be managed very effectively. The advent of new drugs (such as febuxostat and urate oxidase [uricase]) and enhanced understanding of the pathogenesis of gout continue to improve our therapeutic options, particularly in a subset of patients with refractory disease and those who are intolerant to currently available medications.

Gout is a ubiquitous disorder with a growing public health burden. Potentially one of the most successfully managed and most satisfying inflammatory arthropathies to treat, gout is frequently suboptimally treated.[1,2] Gout treatment should be individualised and guided by some important principles.

Gout is a heterogeneous disease resulting from deposition of the end product of purine metabolism, monosodium urate (MSU) crystals, in tissues. Hyperuricaemia is the fundamental pathogenic biochemical aberration upon which various aetiological influences predispose to the expression of the clinical disorder of gout. Emphasis on associated conditions such as hypertension, renal impairment, obesity, insulin resistance and coronary artery diseases[3-6] is warranted to better understand the potential causal role of hyperuricaemia. A diagnosis of gout should lead the clinician to search for unrecognised significant co-mobidities and underlying aetiologies, with the goal of comprehensive gout management.

Although gout is one of the most studied rheumatic diseases and one of the few for which there are reasonably safe and effective long-term disease-modifying therapies, non-adherence and medical errors are common in the management of patients with gout.[1,2,7] Certain groups of patients continue to pose management challenges, such as those with allografts, severe heart failure and renal failure.

When considering therapy for gout, it is important to distinguish between therapy for acute gout, where the goal is to reduce inflammation, and therapy to prevent gout, where the goal is to manage hyperuricaemia. In addition, non-pharmacological approaches such as lifestyle modifications, including dietary interventions and weight management, as well as a reduction in alcohol consumption, should be instituted concurrently. This review provides a clinically orientated guide to the management of acute gouty attacks, and to the prevention and correction of hyperuricaemia. We highlight important subsets of patients and provide a presentation of recent advances that are targeted towards improving the management of gout.

1. Epidemiology

The episodic nature of the symptoms and signs of gout and the diagnostic uncertainty of gout make determination of prevalence and incidence challenging. In the US, 5.1 million people self-reported a diagnosis of gout to a physician, according to the most recent National Health and Nutrition Examination Survey (NHANES III).[8] Gouty arthritis is the most common inflammatory joint disease in men aged >40 years.[9]

Several studies suggest that gout frequency is increasing worldwide. Harris et al.[10] observed a 3-fold increase in gout prevalence in the UK over just 2 decades of follow-up. Similar observations have

been reported from New Zealand in both the native Maori and European populations.[11] Previously, the National Health Interview Survey showed that the prevalence of self-reported gout doubled between 1969 and 1985, but the rate of increase has slowed significantly between 1992 and 1996 (9.4 cases per 1000 persons).[12] In a managed care population, the overall prevalence in 1999 increased by 80% when compared with that in 1990, with the trend of increase mainly for those aged >75 years. Although these trends are very intriguing, data of this type may be confounded by the method used to ascertain prevalence. In contrast, prevalence rates in the younger age groups remained consistently low, overall.[13] Although the sex gap narrows after menopause, men still represent most of the total burden of disease.[13]

Data on incidence are also limited. The annual gout incidence ranges from 8.4 to 14 cases per 10 000 patient-years,[14,15] with cumulative incidence of acute gout over 12 years reaching 36% for those with urate levels of 8 mg/dL or more in the Framingham study. An approximately 2-fold increase in primary gout incidence in the US over the past 20 years was demonstrated.[16] More recently, a study using results from the UK General Practice Research Database showed that the incidence of gout appears to be relatively flat over the past decade.[17]

These potentially changing trends in gout epidemiology may be explained by recently confirmed dietary changes, increased longevity, and increasing numbers of individuals with metabolic syndrome and organ transplants.

2. Risk Factors and Gout-Associated Conditions

2.1 Hyperuricaemia

Hyperuricaemia is the necessary and strongest risk factor for gout but by itself does not inevitably cause clinical gout.[18,19] Epidemiologically determined normal serum urate levels in men and premenopausal women (7 mg/dL [416 μmol/L] and 6 mg/dL [357 μmol/L], respectively) are close to the limits of urate solubility, which is physiologically defined as approximately 6.8 mg/dL.

Depending on the degree of hyperuricaemia and other factors, gout may develop after a varying duration. The higher the initial serum urate level the greater the incidence of a first episode of acute gout arthritis.[17] In a cohort of healthy men followed for 15 years with serial measurement of urate levels, the annual incidence rate of gout was 4.9% with serum urate levels of ≥9 mg/dL. This compares with a 0.5% gout incidence for levels between 7.0 and 8.9 mg/dL and 0.1% for urate levels <7.0 mg/dL.[18]

2.2 Diet and Alcohol

Recent updates from the HPFS (Health Professionals Follow-Up Study) on dietary factors suggest that higher consumption of meat products and seafood conferred a higher risk of incident gout, whereas purine-rich vegetables and total protein did not increase risk. Notably, high dairy intake appeared to be protective.[20]

Data from the HPFS also showed that beer and, to a lesser degree, liquor consumption was strongly associated with increased gout risk in contrast to wine consumption, which did not independently increase risk.[21] Subsequent analysis of NHANES III showed that serum urate levels increased with higher meat, seafood or alcohol intake and decreased with higher dairy intake.[20,22] The high purine content in beer,[23] accelerated adenosine triphosphate (ATP) turnover and reduced renal clearance[24-26] may account for greater risk of gout and hyperuricaemia among heavy beer drinkers.

In addition to alcohol consumption, Lin et al.[27] found an independent association of central obesity with gout in a Chinese population, corroborating a more recent study of a US population demonstrating that adiposity and weight gain were strong risk factors for gout and that weight loss was protective.[4]

2.3 Medications and Toxins

Many drugs and toxins influence nephronal handling of uric acid with unclear mechanisms. Diuretic use has been shown to increase serum urate levels and is a risk factor for incident gout independent of hypertension.[4] Both loop and thiazide diuretics reduce uric acid excretion, presumably by causing mild volume depletion with consequent enhance-

ment of proximal tubular reabsorption. Furosemide, nicotinic acid and pyrazinamide may act directly on urate transporter 1 (URAT1) to enhance urate reabsorption[28] (see figure 1). High dosages of aspirin (>3 g/day) are known to be uricosuric, and widely used mini-dosages (even at 81 mg/day) can cause decreased urate clearance and elevate serum urate levels.[29] Renal transplant recipients who are treated with ciclosporin (cyclosporine), which decreases uric acid excretion,[30] have a very high prevalence of hyperuricaemia (approximately 80%) and an increased risk of gout. Gout develops in up to 10% of individuals within the first few years following transplantation.[31] Chronic lead intoxication (e.g. by consumption of contaminated moonshine) causes hyperuricaemia from tubulointerstitial nephropathy or alteration of the purine metabolism.[32,33]

2.4 Gout-Associated Conditions

There is an increasing interest in the association of hyperuricaemia and gout with several co-morbidities. However, the causal relationship remains to be elucidated.

2.4.1 Hypertension

High serum urate levels are associated with subsequent hypertension.[36-40] However, it has been established prospectively that hypertension is an independent risk factor for incident gout.[4] Recent evidence strongly implicates uric acid as a cause of hypertension because of renal mechanisms independent of crystal deposition in hyperuricaemic rat models.[41,42] Uric acid appeared to activate the renin-angiotensin system and inhibit nitric oxide, leading to glomerular hypertension and renal injury, which were responsive to angiotensin-converting enzyme inhibition.[42] Furthermore, urate lowering by allopurinol can ameliorate new-onset hypertension in adolescents.[43]

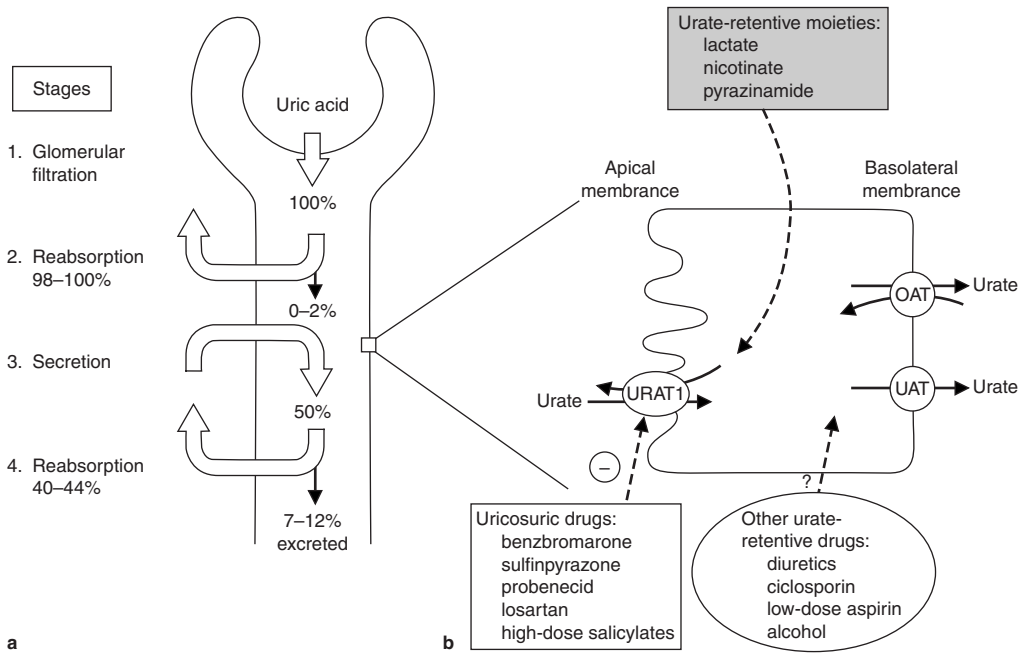

Fig. 1. Nephronal handling of uric acid. (**a**) Four-stage model illustrating bi-directional urate transport at the proximal tubule. Net urate excretion is determined by the final two stages, as discussed in the text. (**b**) Putative mechanisms of the transporters urate transporter 1 (URAT1), organic anion transporter (OAT) and the voltage-sensitive urate transporter (UAT) implicated in the renal reabsorption of urate are depicted. Uricosuric drugs (clear box) suppress URAT1 from the apical side, whereas urate-retentive moieties (shaded box) serve as exchanging anions from the intracellular compartment, thereby stimulating reabsorption. Other clinically important drugs and factors that decrease urate elimination (clear circle) via an unclear mechanism are listed (adapted from Bieber and Terkeltaub[34] and Ichida et al.[35])

2.4.2 Kidney Disease

Extreme hyperuricaemia can directly affect the kidneys. Three types of complications have been described:

- chronic urate nephropathy with crystal deposition in the medullary interstitium;
- acute uric acid nephropathy, which is typically associated with tumour lysis syndrome and occurs when crystals form in the collecting tubules;
- uric acid nephrolithiasis (urolithiasis), which is relatively rare among previously asymptomatic hyperuricaemic individuals, with an annual incidence of 0.4% compared with 0.9% in patients with gout.[18]

The role of hyperuricaemia in renal failure is controversial. Hyperuricaemia has been observed to be an independent predictor of renal failure in healthy individuals.[44] Urate nephropathy may result in inflammation and fibrosis, but rarely leads to renal insufficiency.[45] Hyperuricaemia accelerated renal disease progression in a murine experiment via a mechanism linked to high systemic blood pressure and vascular disease.[46]

2.4.3 Other Conditions Potentially Associated with Gout

Several medical conditions have been associated with hyperuricaemia and gout, including metabolic syndrome, hyperlipidaemia, diabetes mellitus, insulin resistance and cardiovascular disorders, as shown in table I. At this time, treatment of asymptomatic hyperuricaemia alone has not been recommended.[47] If proven pathogenic, large interventional trials will be required to assess the beneficial effects of reversing hyperuricaemia in the course of these co-morbid disorders.

Table I. Common chronic medical disorders associated with hyperuricaemia and gout

Medical disorder	References
Obesity	4,27
Hyperlipidaemia, particularly hypertriglyceridaemia	6,27
Hypertension	3,36-43
Cardiovascular disease	5,14
Chronic renal disease	44,46
Insulin resistance, diabetes mellitus, metabolic syndrome	6,48,49

3. Pathophysiology of Hyperuricaemia and Gout

3.1 Classification

Table II summarises the classification of hyperuricaemia. Distinction between overproducers and underexcreters may have therapeutic as well as investigative significance and can be achieved by measuring daily urinary uric acid excretion. Excretion of urinary urate in excess of 1000 mg/day indicates overproduction, which accounts for 10–15% of patients with hyperuricaemia.[50] Overproduction disorders are generally due to inherited defects of purine nucleotide metabolism, accelerated ATP synthesis or diseases resulting in increased rates of cell turnover.

Underexcretion (urinary excretion of urate <330 mg/day)[51] as a result of reduced urate clearance is responsible for about 85–90% of hyperuricaemia.[50] It is widely misconceived that the underexcretors have a lower rate of urinary uric acid excretion. Although it is true that most patients with gout have a lower fractional urate excretion for any given plasma urate level, the inefficient excretion kinetics obligates a higher serum urate level to drive the necessary normal rate of urinary urate excretion in order to maintain the steady state at which production and clearance are in relative equilibrium.[52] Decreased urate clearance could also be the result of reduced urate filtration, enhanced reabsorption or decreased secretion. Patients with renal impairment, regardless of cause, have diminished excretion of uric acid.[53]

3.2 Purine Metabolism and Uric Acid Excretion/Transport

The homeostasis of blood urate levels is maintained by the balance between purine metabolism and excretion. The enzyme uricase, which degrades urate to allantoin, the end product of purine nucleotide catabolism (see figure 2), is not expressed in humans. Uric acid is synthesised mainly in the liver, and one-third of the daily urate load is derived from degradation of dietary sources, with the remainder from the breakdown of endogenous purine compounds. The degradation of purine nucleotides, guanylic acid, inosinic acid and adenylic acid yields

Table II. Classification of causes of hyperuricaemia[50]

Gout classification		Pathophysiological examples
Increased uric acid production (10% of gout population)		
Primary	Idiopathic	
	Inherited enzyme defects	Hypoxanthine-guanine phosphoribosyl transferase deficiency, phosphoribosylpyrophosphate synthetase deficiency, glucose-6-phosphate deficiency
Secondary	Excessive purine intake	
	Ethanol consumption	
	Drugs	Nicotinic acid, warfarin, chemotherapy (tumour lysis syndrome)
	Myeloproliferative disorders	
	Lymphoproliferative disorders	
	Polycythaemia vera	
	Psoriasis	
Decreased renal clearance of uric acid (90%)		
Primary	Idiopathic	
	Inherited disorder of renal uric acid excretion	Polycystic kidney disease, familial juvenile hyperuricaemic nephropathy, medullary cystic kidney disease
Secondary	Hypertension	
	Chronic renal failure	
	Metabolic abnormalities	Hypothyroidism, hyperparathyroidism, diabetic or starvation ketoacidosis, lactic acidosis, Bartter's syndrome
	Drugs	Diuretics, ethanol, low-dose aspirin (<2 g/day), ciclosporin, tacrolimus, ethambutol, pyrazinamide, levodopa, laxative abuse (alkalosis)
	Lead nephropathy	
	Volume depletion	
	Sarcoidosis	
	Preeclampsia	
	Chronic beryllium disease	

purine bases, guanine and hypoxanthine. Hypoxanthine is then metabolised to xanthine. In the final step, xanthine oxidase acts irreversibly on xanthine to produce uric acid.

Urate elimination in humans is mainly via the kidneys and enteric excretion eliminates one-third of the daily total. Over 95% of the urate is filtered freely at the glomerulus and then reabsorbed almost completely in the early proximal tubule to undergo further tubular secretion and reabsorption (see figure 1a). The final two steps determine the net urate excretion. Half of the reabsorbed urate is actively secreted by the second segment of the proximal tubules, followed by a post-secretory reabsorption of almost all but 7–12% of the filtered urate load.

Transmembrane channels that operate to transport urate in the kidney have been elucidated. URAT1, a novel member of the organic anion transporter (OAT) family, encoded by *SLC22A12*, appears to be the primary urate-anion exchanger that regulates serum uric acid levels. It is localised only in the apical membrane of proximal tubule and mediates urate reabsorption by exchanging luminal urate with intracellular anions (e.g. lactate, nicotinate and pyrazinamide are among the most potent stimulators identified) [see figure 1b]. Uricosuric agents such as probenecid, losartan, sulfinpyrazone, benzbromarone and high luminal salicylate suppress URAT1. Uricosuric drugs suppress URAT1 from the apical side, whereas urate-retentive moieties (lactate, nicotinate and pyrazinamide) serve as exchanging anions from the intracellular compartment, thereby stimulating reabsorption. Mutations in *SLC22A12*, with gene dose effect on serum urate levels, have been identified in familial renal hypouricaemia, which is characterised by severe hypouricaemia, uricosuria and susceptibility to exercise-induced acute renal failure.[28,35] OAT and a

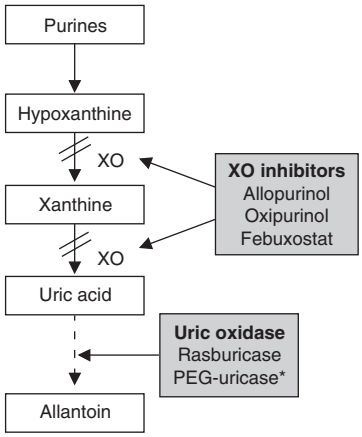

Fig. 2. Simplified schematic diagram of purine catabolism and sites of action of drugs used to lower uric acid in the treatment of chronic gout. The degradation of purine nucleotides (guanylic acid, inosinic acid and adenylic acid) yields purine bases, guanine and hypoxanthine. Hypoxanthine is then metabolised to xanthine. In the final step, xanthine oxidase (XO) acts irreversibly on xanthine to produce the end product, uric acid, in humans. Sites of action of XO inhibitors and uric oxidase analogues are shown. **PEG** = polyethylene glycol. * under development.

ubiquitously expressed voltage-sensitive urate transporter, UAT (also known as galectin 9), support urate reabsorption at the basolateral membrane. Urate secretion at the proximal tubule is putatively mediated by OAT1 and the sodium-dependent phosphate co-transporter, NPT1.[34]

3.3 Pathogenesis of Acute Gouty Attack

The probability of gout arising in a joint/tissue depends not only on the tissue content of urate but also on the pH and temperature of the joint fluid and concentration of other solutes, as well as its macromolecular constituency. The predilection for MSU crystal deposition in osteoarthritic joints may relate to repetitive minor trauma. The paroxysm of acute inflammation and systemic manifestation triggered by free MSU crystals is driven by neutrophil influx and a cascade of humoral and cellular inflammatory mediators. Activation of complement, synoviocytes, mast cells and endothelium induces a myriad of cytokines that culminate in acute synovitis.[34]

4. Clinical Features

Gout is a chronic disease best described in three stages: (i) acute arthritis; (ii) intercritical gout; and (iii) chronic tophaceous gout. Acute gouty flare presents with an abrupt onset of severe monoarthritis often at night, with extreme pain, warmth, swelling and erythaema that crescendo to maximal intensity over 8–12 hours. Fever may occur and, in the elderly, delirium may even be a feature.[54] With first attacks, 90% are monoarticular, half of which involve the first metatarsophalangeal joint (podagra). Common sites of acute flares are the feet, ankles, knees and, less commonly, elbows, wrists and fingers.[55] Extra-articular manifestations such as olecranon and pre-patellar bursitis, as well as tenosynovitis, are also typical. Untreated initial attacks typically subside over 3–10 days. As the inflammation recedes, the overlying skin may exfoliate.

Factors that provoke an acute attack include trauma, surgery, sepsis, intravenous hyperalimentation, alcohol binges, starvation, overindulgence in high-purine foods and the introduction of certain drugs.[50] Drugs such as allopurinol, thiazides and ciclosporin may precipitate gout by rapidly altering urate levels, causing microtophi destabilisation and crystal shedding into synovial fluid.[56]

An asymptomatic phase between attacks is called intercritical gout. Despite clinical quiescence, the disease may continue to advance, with variable shortening of intercritical segments as the body urate stores accumulate. Aspiration of a previously inflamed joint during the intercritical period not uncommonly demonstrates extracellular MSU.[57]

Advanced gout is characterised by chronic destructive arthritis, often with secondary degenerative changes, bony erosions and development of tophi. Flares become polyarticular, additive and ascending, lasting longer with attacks of increasing severity. Chronic polyarticular gout may be confused with rheumatoid arthritis because of the non-remitting pain, inflammation and deformities associated with tophi, which can be mistaken for rheumatoid nodules. Tophi development is a function of early age of onset, long duration of untreated disease and high serum urate levels.[58] Urate crystals may aggregate anywhere over and in the body, but are found most commonly in the finger pads, wrists, pinnae, knees

and olecranon bursae, and over pressure points, e.g. extensor aspect of the forearm and Achilles' tendon. The advent and use of allopurinol and uricosuric agents has led to a general decline of tophaceous gout.[59]

Gout in transplant recipients is more likely to be tophaceous and extra-articular and may affect atypical joints early in its course.[31] It is believed that the glucocorticoids in the immunosuppressive regimen delay overt inflammation until a large urate pool has accumulated.[31]

4.1 Diagnosis and Differential Diagnosis

The definitive diagnosis of acute gout is the demonstration of strongly negative birefringent, needle and rod-shaped MSU crystals (usually intracellular during acute attacks) in synovial fluid or tophaceous tissue under polarised light microscopy.[60] The synovial fluid is inflammatory, with a white blood cell count typically ranging from 5000 to 50 000/μL, predominantly neutrophils. A purulent fluid should always raise the suspicion of septic arthritis as an alternative diagnosis or concurrent pathology, especially in a setting of high fever, leukocytosis, polyarticular involvement, an identified source of infection or multiple co-morbidities (i.e. diabetes, old age and alcohol abuse).[61] Similarly, pseudogout or basic calcium phosphate-induced inflammation is another diagnostic consideration, highlighting the importance of synovial fluid analysis, Gram stain and cultures. In a young patient with a recent history of enteritis or urethritis, reactive arthritis is also a consideration. The intense inflammation of the periarticular soft tissue may also mimic cellulitis. Chronic tophaceous gout may be reminiscent of rheumatoid, psoriatic arthritis or the calcinosis of scleroderma.

A presumptive diagnosis can be made based on the triad of classic inflammatory monoarthritis, hyperuricaemia and a dramatic response to colchicine, but there are several pitfalls with this approach. Gout may first present with a polyarticular and chronic tophaceous form, especially in the elderly. An increasing gout incidence is noted in elderly women, often with mild renal insufficiency, compliance with diuretic therapy and with atypical joint involvement such as in the osteoarthritic nodes of the hands, superimposed with earlier tophi formation.[62] Normouricaemia also does not preclude the diagnosis of gout because up to 40% of patients have normal serum urate levels during attacks.[63] Lastly, other crystal arthropathies also respond to colchicine.

4.2 Additional Investigations

Although it is important to assess the serum urate level, it is neither practical nor useful to estimate urine uric acid excretion in routine practice. Simkin et al.[64] recommended screening out the overwhelming majority of patients with hyperuricaemia who excrete normal amounts of urate on self-selected diets by measuring urate and creatinine in serum and spot, mid-morning urine samples, and calculating urate excretion normalised to a glomerular filtration rate of 100 mL/min. Purine-restricted diets and 24-hour urine collections need then only be considered in those unusual patients in whom the excretion rate in spot urine samples is high.[64] Renal function can be assessed by serum creatinine level or, in the elderly, by creatinine clearance (CL_{CR}) to identify mild chronic renal insufficiency. CL_{CR} is important in guiding medication dose administration. Leukocytosis and elevation of the erythrocyte sedimentation rate are often present in acute gout but are insufficiently specific to add in the differential diagnosis. Blood pressure measurement, fasting blood glucose and a lipid profile are appropriate screening tests for the associated conditions noted in section 2.4.

Plain radiographs contribute little to the diagnosis of acute gout except to confirm soft tissue swelling. However, evidence of first metatarsophalageal joint erosion may occasionally be present, despite absence of an antecedent history. An asymmetric, inflammatory, erosive arthritis (with an 'overhanging' edge), soft tissue nodules and preservation of normal bone mineral density are the radiographic hallmarks of chronic gout.

5. Treatment

5.1 Goals

The treatment goals depend first and foremost on the correct diagnosis of gout. In an acute gout attack, symptomatic pain relief and management of inflam-

mation is paramount, after which preventing future attacks may be necessary. In chronic gout, the focus is on lowering serum urate levels to <6 mg/dL to promote dissolution of urate deposits and prevent further flares.[65,66] Barriers to optimal management include lack of patient education, presence of co-morbid conditions, particularly renal impairment, and the potential for adverse drug reactions.

Table III summarises the usual dosage regimens, special considerations and contraindications of the various pharmacological options according to the stages of gout.

5.2 General Approach

Gout has always been attributed to gluttony, overindulgence in alcohol and food, and obesity. Although a decrease in the serum urate level may be achieved with appropriate lifestyle and dietary changes, diet plays only a modest role in manage-

Table III. Therapeutic agents for acute and chronic gout

Therapeutic agents	Proposed regimen	Considerations
Agents for acute gout		
NSAIDs		
Non-selective COX inhibitors and selective COX-2 inhibitors where appropriate	Maximum or high doses for 2–3 days and tapered over 5–7 days	Consider COX-2 inhibitors in peptic ulcer disease, GI bleed Contraindicated in patients with a history of aspirin or NSAID-induced asthma, renal dysfunction, CHF Interaction with warfarin
Oral colchicine	Begin with 0.5–0.6mg every 6–8 hours Not to exceed 12 tablets per attack	Use with caution in patients with renal or hepatobiliary dysfunction, active infection, age >70 years Drug interactions with ciclosporin, statins, macrolides Use of IV formulation controversial and should be used with extreme caution; can cause local tissue necrosis
Glucocorticoids		
Oral prednisone	30–60 mg/day for 2–3 days, taper over 2–3 weeks	Worsening of glycaemic control in diabetic patients May need to add other anti-inflammatories or use moderate to high doses
Intra-articular (if one or two joints)		Parenteral route if unable to take orally
Methylprednisolone	80–120 mg/day for 1–2 days IV	Toxicities include osteoporosis, weight gain, cataract, diabetes mellitus, hypertension, GI bleed
Cosyntropin	25–40 USP units IM	
Agents for intercritical gout/prophylaxis		
NSAIDs	Lowest effective dosage	NSAID gastropathy (worsens with low-dose aspirin) Renal dysfunction, fluid retention, hypertension, CHF
Oral colchicine	0.6–1.2 mg/day to every other day, adjusted to avoid GI complications Decrease dosage for CL_{CR} <50 mL/min	Reversible axonal neuromyopathy and rhabdomyolysis
Agents for chronic gout		
Xanthine oxidase inhibitor: allopurinol	Starting dosage 100–300 mg/day, titrate upward to achieve goal serum urate Use lower dosages of 100 mg/day or less in elderly patients or those with CL_{CR} <50 mL/min Start with lower dosages (50–100 mg/day) in those with renal impairment	Dyspepsia, headache and diarrhoea are common adverse effects Allopurinol hypersensitivity syndrome is rare but 20–30% mortality Important drug interactions: azathioprine and mercaptopurine
Uricosuric agent: probenecid	Start 0.5 g/d, advance to 1g bid	For underexcretors Must have CL_{CR} >50 mL/min, drink 2L water/day, no history of renal stones, avoid aspirin Toxicities: GI upset, rash, renal stones Drug interactions: ampicillin, salicylates, penicillin, heparin, dapsone, rifampicin, azathioprine

bid = twice daily; **CHF** = chronic heart failure; **COX** = cyclo-oxygenase; **CL_{CR}** = creatinine clearance; **GI** = gastrointestinal; **IM** = intramuscular; **IV** = intravenous; **USP** = United States Pharmacopeia.

ment, and many patients need medications to control the hyperuricaemia.

Implications of recent data (HPFS) for dietary recommendations for patients with hyperuricaemia or gout are generally consistent with the new healthy eating pyramid, except for fish.[67] Curtailing consumption of alcohol, purine-rich meats and seafood, and increasing intake of low-fat dairy products seem prudent recommendations based on accumulating data.[20,21] Contrary to previous beliefs, purine-rich vegetables and a high-protein diet (a proxy for purines) may not need to be avoided.[20] A low-purine diet will lower serum urate by approximately 60 μmol/L (1 mg/dL).[51] Purine-depleted diets were used in the past but may be impractical because of difficulty with adherence.[68]

Weight reduction and lipid control should also be strongly advocated.[69] In a small open-label interventional study of 13 gout patients, a calorie-restricted, low-carbohydrate diet with proportionally higher levels of protein and unsaturated fats was associated with a decline in weight and urate and lipid levels and a concomitant decline in gout flares. An improved diet may promote insulin sensitivity, reduce plasma insulin levels and improve renal urate excretion.[69]

Heightened awareness of medication effects on serum urate levels allow fine-tuning of management of gout in a setting of co-morbidities or intolerance to urate-lowering therapy. Because of the urate-retentive properties of thiazide diuretics, alternative antihypertensive options may be considered in patients with refractory gout if medically plausible.[70] Losartan specifically has a renal uricosuric effect, making it an attractive option for patients with hypertension and renal disease,[34] and it may even be cardioprotective.[71] Fenofibrate has a mild uricosuric effect, which can be taken advantage of if it is otherwise required for the management of hyperlipidaemia.[72]

5.3 Termination of Acute Flare

Resolution of an acute gout flare is aimed at controlling crystal-induced inflammation and pain but by itself is not a cure of gout. The challenge to acute gout flare management is rapid initiation of therapy, determining appropriate duration and dose administration of therapy. Because the episode may be prolonged or worsened as urate levels fluctuate, urate-lowering agents should not be initiated, changed or discontinued (if already taken) as long as gout inflammation persists.[73]

5.3.1 Oral NSAIDs

When not contraindicated, the first line of therapy for acute gout flare is an NSAID. Although, historically, indometacin (indomethacin) has been used, multiple other NSAIDs are also efficacious.[74,75] However, it is necessary to avoid low-dosage salicylate preparations. NSAIDs are an effective method of ameliorating gout flares but they have numerous adverse effects that can limit their use in a particular patient. NSAIDs should be used with caution, and toxicities monitored, in high-risk populations such as the elderly, those with renal impairment, congestive heart failure, liver disease or peptic ulcer disease and those who use anticoagulants.[76,77] A potential substitute for NSAID-intolerant patients are the selective cyclo-oxygenase (COX)-2 inhibitors. Etoricoxib, a COX-2 inhibitor available in Europe but not in the US, has similar efficacy as indometacin in the treatment of gout and causes fewer drug-related adverse effects.[78] However, it should be noted that COX-2 inhibitors have been under increased scrutiny because of concerns about adverse cardiovascular outcomes.[79,80]

5.3.2 Colchicine

Oral colchicine at low dosages of 0.5mg or 0.6mg three to four times a day is sufficient to control the symptoms of acute gout when NSAIDs are contraindicated. Because colchicine interferes with neutrophil phagocytosis and chemotaxis, it is most effective when started within 24 hours after the onset of an attack of gouty arthritis, before these factors have contributed much to the articular inflammatory process. Moreover, the beneficial effect of colchicine declines progressively the longer that treatment is delayed.[81] Colchicine has a narrow benefit-to-toxicity ratio so it must be used carefully, particularly if administered intravenously. Gastrointestinal (GI) adverse effects such as diarrhoea, nausea and vomiting are ubiquitous even at lower dosages and warrant discontinuation of the drug. However, the most serious potential adverse effects are neutropenia and neuromyopathy. Inappropriately high dosages of

colchicine (oral or intravenous) can lead to significant reactions (leukopenia, pancytopenia, disseminated intravascular coagulation and multi-organ failure), which can be life threatening.[82,83] Myoneuropathy has been reported, with or without concomitant use of HMG-CoA reductase inhibitors (statins) or ciclosporin, in patients with CL_{CR} <50 mL/min.[19,84] Colchicine should be used with extreme caution in patients with leukopenia and in those with significant hepatic or renal impairment. Intravenous colchicine has a very high potential for both immediate (e.g. skin necrosis) and short- to moderate-term toxicity (bone marrow suppression) and should seldom, if ever, be used. The intravenous dosage should not exceed 2mg for a single gout attack.[85,86]

5.3.3 Glucocorticoids and Corticotropin

Glucocorticoids and corticotropin (adrenocorticotropic hormone [ACTH]) are also useful for treatment of the disease, particularly where NSAIDs and colchicine are ineffective or contraindicated. Their anti-inflammatory action leads to symptomatic improvement.[87,88] Administering intra-articular glucocorticoids after joint aspiration is a treatment of first choice when one or two joints that can be easily aspirated are involved. Oral prednisone at moderate doses of 30–60mg, or its equivalent, tapered over 2–3 weeks usually allows improvement within the first 12–24 hours and resolution in 7–10 days.[87] Systemic glucocorticoids, although efficacious, have the potential for serious adverse effects such as osteoporosis and increased risk of infection if used long term or at high dosages.

Corticotropin is a further consideration for patients who have multiple medical problems and have contraindications to first-line gout therapies. However, its use is limited by cost, availability and comfort to the patient (intramuscular administration). The exact mechanism of action in gout is unknown but it is thought to stimulate adrenal hormones that produce an anti-inflammatory effect.[89] Corticotropin has been shown to relieve pain within 3–4 hours.[90] Adverse effects include mild hypokalaemia, hyperglycaemia, fluid retention and rebound arthritis.[91]

5.4 Protection against Further Flares

In order to avert future attacks, prophylactic agents such as NSAIDs and colchicine should be considered for the medium term. These therapies will help reduce the frequency and severity of gout flares,[92] but additional drugs are required to stop the damage caused by hyperuricaemia and urate crystal deposition. These drugs also aid in reducing rebound flares that occur after the initiation of urate-lowering therapies such as allopurinol.[93]

To minimise the risk of adverse effects, the lowest effective dosage of an NSAID should be used for protection against an acute flare. The colchicine prophylaxis dosage typically ranges from 0.6mg to 1.2mg daily, adjusting for GI complications. The colchicine dosage must be adjusted according to renal function and long-term use should be avoided because of the rare complication of myopathy, although there is no specific recommended timeframe. Colchicine myotoxicity has been reported after variable duration of therapy ranging from 4 days to 11 years (mean of 40 months) in 82 documented cases.[94]

5.5 Treating Hyperuricaemia and Preventing Disease Progression

Chronic urate-lowering therapy is cost effective in patients who have more than two gout flares a year or in individuals with gouty complications.[51] The goal of treatment is to lower serum urate levels, without drug toxicity, to <6.0 mg/dL. By achieving mean urate levels <6.0 mg/dL, there are significantly fewer acute flares, fewer crystals in joints and a reduction in tophi size.[65,66,95,96]

Chronic gout therapy should be deferred until the acute attack resolves, and it should only be initiated with concurrent prophylactic NSAIDs or colchicine to reduce possible rebound flares.[73] Prophylaxis is continued until the patient is attack free with stable serum urate levels <6.0 mg/dL typically for 3–6 months. It is very important to educate the patient about potential flares, despite the use of prophylaxis, and the fact that urate-lowering therapy is considered to be lifelong. Intermittent dose administration or withdrawal of these agents leads to a vicious cycle of acute attacks. Approved urate-lowering

agents for gout include xanthine oxidase inhibitors and uricosuric agents.

5.5.1 Xanthine Oxidase Inhibitors

The xanthine oxidase inhibitor allopurinol is most commonly used in the treatment of chronic gout because it is efficacious for both underexcretors and overproducers. It is the treatment of choice for overproducers, tophaceous gout, nephrolithiasis or urate nephropathy, and in patients with renal insufficiency. Allopurinol and oxipurinol (oxypurinol) lower serum urate and urine uric acid levels. Starting allopurinol at 100 mg/day and slowly titrating upward towards or above 300 mg/day anecdotally may limit post-therapy flares and hypersensitivity reactions. Allopurinol 300 mg/day reduces serum urate levels to normal values in 47–85% of patients with gout, and in some patients a dosage of 100–200 mg/day is adequate.[97-99] The dosage can be increased by 100 mg/day with periodic measurements of serum urate levels to dosages as high as 800 or even 1000 mg/day in order to achieve the target level. It is paramount to check for compliance before escalating the dosage, as almost half of patients taking allopurinol for gout do not take the dosage as prescribed.[100] Dosages of 50–100 mg/day are alternatively initiated in the elderly or if CL_{CR} is <50 mL/min.[51]

Adverse effects associated with allopurinol include rash, diarrhoea, leukopenia, pruritus and fevers. There is a very rare dose-dependent hypersensitivity reaction that can cause up to 20% mortality.[101] The syndrome includes eosinophilia, rash, renal and hepatic dysfunction, and vasculitis. Patients with renal insufficiency or receiving diuretic therapy are at higher risk.

A strategy for treating allopurinol-intolerant gout patients is to switch to uricosuric drugs (described in section 5.5.2). Resistance to allopurinol may require dosage increases above the traditional range and may be due to non-adherence. Combination treatment with allopurinol and uricosuric drugs may be considered, but there is little evidence supporting this approach. If a patient is unable to switch to a uricosuric drug, allopurinol desensitisation can be considered.

In patients with hypersensitivity, there are methods available for allopurinol desensitisation. Daily escalation of dose from 8mg to 300mg over 30 days can successfully desensitise the patient.[102] A quicker intravenous method, usually reserved for patients who do not respond to oral desensitization, is possible.[103] Oxipurinol, where available, can be given to patients who do not respond to desensitisation or who have a recurrence of allopurinol hypersensitivity after desensitisation.[104]

5.5.2 Uricosuric Drugs

Uricosuric agents reverse the most common physiological abnormality in gout. Probenecid and benzbromarone (available in Europe but not in the US) increase uric acid excretion in urine via the renal uric acid anion transport pathway (figure 1b). These treatments should only be used in patients who underexcrete uric acid (<800mg over 24 hours). They must be started at low dosages and gradually titrated upward as the effects of these drugs will cause gross uricosuria, which may lead to urinary stones. An appropriate candidate for a uricosuric agent is an individual who can consistently imbibe at least 2 litres of fluid daily and who is willing to take multiple daily doses of medication. Alkalinisation of urine may also be required to prevent stones. Therapy with uricosuric drugs should be avoided in patients who have known nephrolithiasis[105] and in those taking low-dose aspirin, which can counteract the uricosuric effects.[19] Patients with renal dysfunction (CL_{CR} <50 mL/min) will not benefit from this therapy. Adverse effects of probenecid include rash, GI intolerance, precipitation of an acute attack of gout and nephroureterolithiasis. In the setting of polypharmacy, another limitation of probenecid is its multiple drug-drug interactions (particularly with azathioprine) as a result of altered metabolism or elimination of these other agents.

5.6 Novel Therapeutics

Given the various limitations of current drugs used to treat gout, the development of new treatments is warranted for patients with chronic gout who are intolerant of, or refractory to, available therapy for controlling hyperuricaemia.

5.6.1 Febuxostat

Febuxostat is an orally administered, non-purine, selective xanthine oxidase inhibitor that appears to be more potent than standard-dose allopurinol at

lowering serum urate levels.[106] Because it is metabolised by the liver, it can be used for those patients who have renal insufficiency.[107,108] A phase III, randomised, double-blind trial showed that febuxostat (80mg, 120mg) was more effective than allopurinol 300mg in lowering serum urate levels to <6.0 mg/dL. There was a significant increase in initial gout flares in the high-dose febuxostat group compared with allopurinol, but this might have been a result of inadequate prophylaxis for rebound gout flare upon initiation of urate-lowering therapy. Over the 52-week trial, similar reductions in gout flares and tophus reduction occurred in all groups.[109] Long-term studies are ongoing to provide further information about the longer-term efficacy and safety profile of febuxostat. Febuxostat has been submitted for European and US regulatory approval for management of hyperuricaemia in chronic gout.

5.6.2 Urate Oxidase (Uricase)

Urate oxidase (uricase) facilitates the conversion of uric acid into allantoin, which is a more soluble molecule. A non-recombinant form has been isolated from *Aspergillus flavus* (rasburicase), which has been used effectively in tumour lysis syndrome. Unfortunately, when given intravenously this drug can cause severe immunogenic reactions (anaphylaxis).[110,111] PEGylation of uricase seems to increase the half-life of this drug and lower its immunogenicity, making it a potential option in the treatment of gout.[112,113] Subcutaneously administered polyethylene glycol (PEG)-uricase has been shown in a phase I study to be well tolerated and to significantly lower serum urate levels in refractory gout patients, but antibodies against PEG-uricase were noted, which may limit its efficacy.[114] A phase II study demonstrated efficacy of the drug but with infusion reactions in nearly half of patients without anaphylactic reactions.[115] PEG-uricase is under development and is currently undergoing phase III clinical trials examining its effects on joint pain and serum urate levels in patients with gout.

6. Special Considerations

6.1 Transplant Recipients with Gout

Gout can particularly be a problem in allograft recipients taking calcineurin antagonists (ciclosporin and tacrolimus). These drugs raise serum urate levels by increasing renal tubular absorption,[116] and are associated with hypertension and reduced glomerular filtration.[117] Close to 80% of patients treated with ciclosporin become hyperuricaemic and 10% develop gout.[118] Renal impairment often limits colchicine and NSAID use. Concomitant use of azathioprine, which is a common immunosuppressant, and allopurinol should be avoided if possible. Allopurinol inhibits xanthine oxidase, which degrades the active metabolite of azathioprine, mercaptopurine (6-mercaptopurine). Increased plasma mercaptopurine levels may result in potentially fatal bone marrow suppression.[119] A dose reduction to approximately 25% of the normal dose of azathioprine[51] is warranted when no other urate-lowering options exist and when azathioprine must be concomitantly used with allopurinol therapy. The patient's blood count should be monitored assiduously. An alternative to azathioprine is mycophenolate mofetil, which inhibits purine synthesis and is unaffected by allopurinol in its metabolism.[120] Systemic or intra-articular glucocorticoids for gout flares are frequently necessary for this challenging population.

6.2 Elderly Patients

The adverse effects of certain treatments can, at times, outweigh the benefits of gout therapy, particularly in the elderly. Optimising conservative measures are often helpful in the elderly population, e.g. resting and icing an affected joint and reducing alcohol and purine intake. When medically feasible, stopping medications such as diuretics may also benefit the elderly patient.[61]

Often in the case of acute gout flares in the elderly (aged >75 years), a short course of oral glucocorticoids may be safer and more useful than an NSAID. NSAIDs have the potential of causing acute renal failure as well as GI bleeding. COX-2 inhibitors may reduce GI complications but renal adverse effects can still occur.[121] Colchicine is

Table IV. A comprehensive approach to the evaluation and management of patients presenting with gout

Establish accurate diagnosis. Attempt diagnostic arthrocentesis for crystal confirmation
Educate patients about the disease, precipitating factors, lifestyle changes and rationale of using various drugs
Evaluate patients for co-morbidities and underlying aetiologies linked to hyperuricaemia (e.g. diuretic use), and modify where reversible and plausible
Symptomatic control of acute attack with NSAIDs or colchicine is generally effective but should be tailored to patients' renal function and co-morbidities. Glucocorticoids are an alternative when NSAIDs and colchicine are contraindicated
Hypouricaemic agents should be started in patients with frequent attacks, tophi or chronic arthropathy. After subsidence of acute flare, use adjunct of prophylactic NSAIDs or colchicine when starting urate-lowering therapy. The dosage should be increased to achieve a target serum urate of <6 mg/dL
Recognise drug interactions and monitor for potential toxicities in high-risk populations such as the elderly and those with renal or hepatic impairment
Consult a rheumatologist or other gout specialist when managing patients with atypical or refractory gout

often poorly tolerated in the elderly population for acute attacks but may still be used for prophylactic treatment.[122] To lower serum urate levels, allopurinol is the preferred drug for the elderly because of age-related declines in renal function. As mentioned in section 5.5.1, the starting dosage is usually 50–100 mg/day, as hypersensitivity reactions can be a greater risk if the dosage is not appropriately adjusted for renal function.[123]

6.3 Renal Insufficiency

In an acute gout attack, systemic or intra-articular glucocorticoids are helpful in aborting an attack in this setting. NSAIDs are contraindicated but colchicine may still be used judiciously in mild renal impairment (e.g. 0.6mg every 2–3 days), based on expert opinion.[124] Colchicine should not be administered in patients with a CL_{CR} <10 mL/min.

The choice of urate-lowering drug is limited in individuals with significant renal impairment. Probenecid has little effect in patients with a CL_{CR} <50 mL/min. Allopurinol is generally considered the optimal therapy for chronic gout in the setting of renal insufficiency. Although it is common practice to adjust the starting dosage of allopurinol according to CL_{CR} to reduce the risk of severe toxicity,[101] some patients may need higher maintenance dosages to achieve a target serum urate level of <6 mg/dL and to halt disease progression. Despite these rough guidelines, among patients who received higher allopurinol maintenance dosages than those normally recommended based on CL_{CR}, no increase was seen in adverse reactions to allopurinol.[125] The dosage of allopurinol should be titrated upwards with caution in patients with renal insufficiency.

7. Recommendations and Conclusion

The incidence and prevalence of hyperuricaemia and gout appear to be increasing, in part reflecting the increasing problems of obesity and metabolic syndrome in an aging population. Although the disease has been well studied, its pathogenesis is increasingly well understood, and a number of effective treatment options exist, many gout patients still progress to develop chronic destructive arthropathy. Medical errors and ineffective treatment, including inadequate patient education on medical and lifestyle risk factors and the correct use of medications, are common pitfalls to safe and successful management. Individualised diagnostic and treatment plans should be guided by the important principles that are outlined in table IV. As advances are made in further translating research into practice and as further new therapies offer even more treatment options, the prognosis of this ancient disease will continue to improve.

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