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REVIEW ARTICLE

Management of gout and hyperuricemia: Multidisciplinary consensus in Taiwan

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Abstract

Gout is an inflammatory disease manifested by the deposition of monosodium urate (MSU) crystals in joints, cartilage, synovial bursa, tendons or soft tissues. Gout is not a new disease, which was first documented nearly 5,000 years ago. The prevalence of gout has increased globally in recent years, imposing great disease burden worldwide. Moreover, gout or hyperuricemia is clearly associated with a variety of comorbidities, including cardiovascular diseases, chronic kidney disease, urolithiasis, metabolic syndrome, diabetes mellitus, thyroid

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dysfunction, and psoriasis. To prevent acute arthritis attacks and complications, earlier use of pharmacotherapeutic treatment should be considered, and patients with hyperuricemia and previous episodes of acute gouty arthritis should receive long-term urate-lowering treatment. Urate-lowering drugs should be used during the inter-critical and chronic stages to prevent recurrent gout attacks, which may elicit gradual resolution of tophi. The goal of urate-lowering therapy should aim to maintain serum uric acid (sUA) level <6.0 mg/dL. For patients with tophi, the initial goal can be set at lowering sUA to <5.0 mg/dL to promote tophi dissolution. The goal of this consensus paper was to improve gout and hyperuricemia management at a more comprehensive level. The content of this consensus paper was developed based on local epidemiology and current clinical practice, as well as consensuses from two multidisciplinary meetings and recommendations from Taiwan Guideline for the Management of Gout and Hyperuricemia.

Key words: gout, hyperuricemia, urate-lowering agents.

Gout is a modern-day disease caused either by reduced excretion (70–90%) or increased production (10–30%) of uric acid that results in elevated serum uric acid (sUA) levels. It is an inflammatory disease manifested by the deposition of monosodium urate (MSU) crystals in joints, cartilage, synovial bursa, tendons or soft tissues. Gout is prevalent in men of middle-age and women after menopause; overall, men comprise 90–95% of the gout population. Acute gout attack is characterized by sudden onset of redness, swelling, warmth and pain in the joints, predominantly those of the lower limbs. Hyperuricemia, defined as a sUA level > 7.0 mg/dL, is the most dominant factor in gout development. The chance of gout development is correlated with sUA levels, as well as the duration of sUA elevation. However, the majority of the hyperuricemic individuals is and remains asymptomatic through their lives and only around 10% of them eventually develop gout. Giving that approximately one-third of patients have normal sUA levels during acute flare of gouty arthritis, patient history, clinical manifestation, disease course, and triggering factors should all be considered in differential diagnoses. Gout diagnosis can be confirmed by joint fluid examination and identification of needle-shaped, phagocytosed MSU crystals in the synovial fluid aspirated during acute flares.

The prevalence of gout has increased globally in recent years, imposing great disease burden worldwide.[1] According to Taiwan's National Health Insurance (NHI) Research Database, the estimated prevalence (based on International Classification of Diseases-9 definition) and incidence of gout in Taiwan was 6.24% and 2.74 per 1000 person-years in 2010, respectively.[2] In a recent nationwide survey (the Nutrition and Health Survey in Taiwan), researchers reported gout prevalence to be 8.2% in men and 2.3% in women in the period from 2005 to 2008,[3] which is close to the estimates for 2004 based on the information derived from the National Health Insurance Research Database (NHIRD).[4] Nevertheless, new treatment agents have transformed the treatment strategies for gout and hyperuricemia. While the inflammatory mechanism of gout has become better understood, evidence supporting the association of gout and hyperuricemia with a wide variety of disorders has grown more compelling. In light of these recent advancements and the fact that comorbidities are highly prevalent in patients with gout or hyperuricemia, two multidisciplinary meetings were held in 2016 to facilitate dynamic exchanges of clinical experience and expertise among medical professionals from the fields of allergy, immunology, rheumatology, cardiology, endocrinology, and nephrology in Taiwan.

METHODS

The following content was developed based on the meeting consensus, as well as the recommendations from the 2006, 2013 and 2016 versions of Taiwan Guideline for the Management of Gout and Hyperuricemia. The target audience for this guideline includes all clinicians, and the target patient population includes adults with acute or recurrent gout. With the approval of the Taiwan Rheumatologist Association (TRA) executive committee, the modulator (KY) along with two co-modulators (JC and TH) of the 2006 and 2013 guideline task force formed a working group to elaborate the 2006 and 2013 TRA recommendations for the management of gout.

Systematic literature searches were conducted by KY, JC and TH using MEDLINE, PubMed, EMBASE, Cochrane Central Register of Controlled Trials and manual searches of the reference lists of the selected

articles. Members of the guideline working group were asked to give an extensive discussion and deliberation for the management of gout based on available research evidence and their own clinical expertise after reviewing the published recommendations.

Prior to the formulation of the 2016 multidisciplinary consensus recommendations, the evidence generated by the TRA was reviewed by a representative panel of nine rheumatologists together with two cardiologists, one nephrologist, one endocrinologist and one general practitioner, who are experts in gout and hyperuricemia, from 12 hospitals around Taiwan to create local recommendations relevant to the diagnosis and management of gout in this country. Finally, the moderators selected 14 key clinical questions pertinent to the diagnosis and management of gout based on previous versions of the TRA gout guideline and discussions through e-mail or physical meetings for gout and hyperuricemia. Owing to time constraints, one final recommendation was determined via an e-mail survey of all rheumatologists who participated in the meeting for TRA guideline production. Individual statements for the 14 clinical questions with level of evidence, grade of recommendation, and level of agreement were developed. The level of evidence and grade of recommendation were scored using the Oxford Centre for Evidence-based Medicine Level of Evidence (2011).[5] The level of evidence (LoE) in support of each recommendation was determined ((i) meta-analysis of randomized controlled trials; (ii) randomized trials or observation studies with dramatic effect; (iii) non-randomized trial controlled cohort/follow-up studies; (iv) case series, case-control studyies or historically controlled studies; (v) mechanism-based reasoning).[5] The grade of recommendation (GoR) was determined (A: consistent level 1 studies; B: consistent level 2 or 3 studies, or extrapolations from level 1 studies; C: level 4 studies or extrapolations from level 2 or 3 studies; D: level 5 evidence or inconsistent or inconclusive studies of any level).[5] Subsequently, a modified Delphi exercise was conducted to determine the level of agreement of each statement. Agreement relates to the entire statement for each recommendation and was voted on a scale from 0 to 10 (0, completely disagree; 10, fully agree).

1. Hyperuricemia Is a Major Risk Factor for Gout ([LoE: 3; GoR: B; Agreement: 9.80 ± 0.40)

Hyperuricemia is a major risk factor for gout. The association between hyperuricemia and gout incidence rate has been reported in the Normative Aging Study;[6] with a sUA level < 7.0, 7.0–8.9 and ≥ 9.0 mg/dL, the annual incidence rate of gout was estimated to be 0.1%, 0.5% and 4.9%, respectively. In a retrospective report, the odds ratio for a gout flare in British gout patients with a sUA level of 6.0–7.0, 7.0–8.0, 8.0–9.0 and ≥ 9.0 mg/dL was 1.33, 1.49, 1.71 and 2.15, respectively, compared with those in whom sUA levels were < 6.0 mg/dL.[7] Although hyperuricemia has been identified as the key risk factor for gout, gouty arthritis only develops in one-tenth of the hyperuricemic patients in clinical observations.[8,9]

2. Gout or Hyperuricemia Is Clearly Associated with a Variety of Comorbidities, Including Cardiovascular Diseases, Chronic Kidney Disease (CKD), Urolithiasis, Metabolic Syndrome, Diabetes Mellitus, Thyroid Dysfunction and Psoriasis (LoE: 3; GoR: B; Agreement: 9.25 ± 0.62)

Cardiovascular diseases

A significant correlation between hyperuricemia and cardiovascular diseases has been demonstrated in an ample amount of studies. For instance, elevation of sUA level has been shown to be significantly associated with both coronary heart diseases (CHD) and heart failure.[10] Even for patients at low risk for atrial fibrillation, hyperuricemia could considerably increase the risk of stroke, indicating that it was also an independent risk factor for stroke for this specific subgroup.[11]

In an American study, male gout patients were reported to experience a 60% excess of CHD and develop angina pectoris twice as often than those without gout.[12] Compared with gout-free patients, the risk of all-cause and cardiovascular mortality in male gout patients was increased by 28% and 55%, respectively.[13] In 2015, analyses of Taiwan's NHI Research Database revealed that gout patients had a 66% greater risk of deep vein thrombosis (DVT), and a 53% increased risk of pulmonary embolism (PE), compared with gout-free patients. Moreover, for gout patients who do not receive urate-lowering agents, their risks of DVT and PE are drastically increased, with a hazard ratio of 2.16 and 2.28, respectively.[14] A nationwide cohort study from Taiwan also found that gout patients had a greater risk of erectile dysfunction relative to the general population.[15]

CKD and nephrolithiasis

In a meta-analysis, gout was proven to be an independent risk factor for CKD (relative risk [RR] = 2.41)

and nephrolithiasis (RR = 1.77), and the authors thus recommended that gout patients should undergo regular screenings for CKD.[16] Research has shown that hyperuricemia may cause kidney damage, thereby accelerating CKD progression. Studies have also demonstrated that urate-lowering agents can have protective effects on renal function in asymptomatic hyperuricemic patients;[17,18] however, the specific underlying mechanism awaits further illustration.[19] On the other hand, the prevalence of gout in CKD patients was also higher than that of the general public.[20] Hyperuricemia was a risk factor for all-cause and cardiovascular mortality in patients with CKD stages 3–5.[21]

Metabolic syndrome

The recent increase in hyperuricemia and gout prevalence may be associated with the surging rates of obesity and metabolic syndrome in recent decades.[7,22,23] In 2013, a report from Taiwan showed that gout incidence rate was increased when hyperuricemia was comorbid with certain metabolic disorders (e.g., hypertension, obesity and hyperlipidemia).[22] Metabolic syndrome is universally a valuable indicator for gout attack in male patients. The risk of gouty arthritis flare in male patients with metabolic syndrome was increased by around 37% even when their sUA levels lie within the normal ranges.[22] However, such correlation was less conspicuous in female patients.[22]

The significant association between sUA level and metabolic syndrome was established in two studies in 2015.[10,23] By enrolling patients with dyslipidemia, one of these studies found that patients with highest sUA category (men: > 7.1 mg/dL [> 420 μmol/L]; women: > 6.1 mg/dL [> 360 μmol/L]) had a significantly higher risk of developing metabolic syndrome, compared with those with lowest sUA category (men: < 4.7 mg/dL [< 280 μmol/L]; women: < 3.9 mg/dL [< 230 μmol/L]).[10] A similar observation was reported in the other Taiwanese local study: compared with individuals with sUA < 7 mg/dL, the risk of developing metabolic syndrome was five times higher among those with sUA > 9 mg/dL.[23]

Diabetes mellitus

As shown in studies, sUA level was not only associated with the risk of diabetes, it was also an independent predictive factor for diabetes complications (e.g., neuropathy, retinopathy, kidney diseases, diabetes mellitus foot and vasculopathy).[24]

Thyroid dysfunction

An article published in 2014 revealed that gout incidence was significantly higher in patients with hyperthyroidism or hypothyroidism than those with normal thyroid function.[25]

Psoriasis

Compared with those without psoriasis, psoriasis patients were at a higher risk of hyperuricemia (RR = 1.37) and gout (RR = 1.83). However, evidence remains inadequate to demonstrate whether psoriasis could be an independent risk factor for gout and hyperuricemia.[26]

3. The Physiochemical Definition of Hyperuricemia Is a Fasting sUA Level > 6.8 mg/dL for Both Adult Males and Females. (LoE: 3; GoR: B; Agreement: 8.40 ± 2.06])

Based on the pathophysiology of gout, the physiochemical definition of hyperuricemia should be defined as a sUA level > 6.8 mg/dL for adults.[27,28] Gout is a disorder that manifests as a spectrum of clinical and pathological features built on a foundation of an excess body burden of uric acid, manifested in part by hyperuricemia, which is defined as a serum urate level greater than 6.8 mg/dL.[28] For easier memorization, a serum urate level above 7.0 mg/dL is considered abnormal in this document. For individuals with a sUA level between 7 and 8 mg/dL, detailed patient history and further physical examination should be performed to confirm the presence of associated disorders such as gout, hypertension, diabetes, obesity and metabolic syndrome (Table 1). Although hyperuricemia is usually asymptomatic, it is imperative for physicians, nurses, pharmacists, physical therapists and nutritionists to conduct in-depth investigations. Hopefully such active measures can facilitate early diagnosis, treatment and prevention of the associated diseases before the target organs are functionally damaged.

4. Immediate Urate-Lowering Therapy Is Not Required for Asymptomatic Hyperuricemia. Potential Causes of Hyperuricemia Should Be Identified and Properly Managed, Especially in Cases Where Metabolic Syndrome-Associated Diseases May Potentially Increase Cardiovascular Risks. (LoE: 3; GoR: B; Agreement: 8.80 ± 1.25)

Hyperuricemia is merely a biochemical disorder. Restoration of sUA levels to normal ranges is possible either by adopting lifestyle changes such as increased

Table 1 Disorders and risk factors associated with hyperuricemia and gout

1. Hyperuricemia — the major risk factor for gout
2. Other disorders
Renal diseases (e.g., CKD, nephrolithiasis, familial juvenile hyperuricemic nephropathy, polycystic kidney disease, medullary cystic kidney disease)
Cardiovascular diseases (e.g., CHD, heart failure, atrial fibrillation, erectile dysfunction, hypertension)
Metabolic syndrome
Psoriasis
Obesity
Lead poisoning
Malignant diseases
Hemolytic disorders
Sickle cell anemia
Tissue hypoxia
Salt restriction
Dehydration
Starvation
Lactic acidosis
Diabetic ketoacidosis
Hyperparathyroidism
Hyperthyroidism/ hypothyroidism
Diabetes insipidus
Toxemia of pregnancy
Chronic beryllium disease
Sarcoidosis
Bartter's syndrome
Down syndrome
HGPRT deficiency
PPRP synthetase overactivity
Glycogenosis I, III, V, VII
3. Drugs and diet
Low-dose aspirin (< 2 g/day)
Diuretics (thiazide and loop diuretics)
Pyrazinamide
Ethambutol
Cyclosporine
Nicotinic acid
Levodopa
Cytotoxic drugs
Laxative abuse (alkalosis)
Methoxyflurane
Tacrolimus
Fructose
Pancreatic extracts
Excessive purine intake of animal origin: meat, seafood
High alcohol (ethanol) intake: beer, spirits

CKD, chronic kidney disease; CHD, coronary heart disease; HGPRT, hypoxanthine-guanine phosphoribosyl-transferase; PPRP, 5-phospho-α-d-ribosyl-1-pyrophosphate.

exercise activity, fluid intake and diet adjustment, or identifying and rectifying the causes of hyperuricemia. However, if hyperuricemia persists, the possibility of gout significantly increases with sUA concentration. Notably, the majority of patients with hyperuricemia (90%) may not experience gout attacks,[6,8,9,29] especially in those with slightly elevated sUA levels. In addition to high sUA levels, the risk factors for gout include obesity, weight gain, drinking habits, hypertension, renal impairment, family history of gout and use of diuretics.[30,31] While asymptomatic hyperuricemia does not require immediate urate-lowering treatment, potential causes of hyperuricemia should be identified and properly managed (Table 1), especially in cases where metabolic syndrome-associated diseases may potentially increase cardiovascular risks. The use of medication such as aspirin, alcohol, diuretics, anti-tuberculosis drugs, cyclosporine[32] and chemotherapy agents may lead to elevated sUA levels in a minority of cases.

5. The Initial Phase of an Acute Gouty Arthritis Often Involves a Single Joint, and the Main Clinical Manifestations Are Characterized by Intense Joint Pain, Redness, Swelling, Warmth and Pain in the Joint and Surrounding Soft Tissues. Fever and Arthritis Attack in Multiple Joints May Occur in Later Phases. (LoE: 3; GoR: B; Agreement: 8.85 ± 1.06)

The initial phase of an acute gouty arthritis often involves a single joint, and the main clinical manifestations are characterized by intense joint pain, redness, swelling, warmth and pain in the joint and surrounding soft tissues. Fever and arthritis attack in multiple joints may occur in later phases. Gout attacks are characterized by the sudden onset of pain, frequently at midnight or before dawn, and some patients may experience premonitions such as slight or stinging pain.[27,33,34] The pain peaks within 1–2 days and usually subsides within 3–10 days even without treatment but may last, although rarely, for a couple of weeks.[27,34,35] Acute gouty arthritis commonly involves the lower distal joints, and the joints most frequently affected in the initial attacks are the first metatarsophalangeal joints, followed by the ankle joints and knee joints. If the sUA level persistently remains above normal ranges, the frequency of acute gouty arthritis generally increases along with time, as crystals may form and precipitate within articular cavities after a period of time.

6. If Chronic Hyperuricemia Is Left Untreated, Tophi (MSU Crystals) May form Subcutaneously and Within the Joints of Gout Patients, Sometimes Resulting in Joint Deformity and Even Loss of Motion in Severe Cases. Tophi May Deposit in the Ear, Subcutaneous Tissues, Joints, Cartilage, as Well as in Kidneys, in Turn Compromising Renal Functions. (LoE: 3; GoR: B; Agreement: 9.25 ± 0.83)

If chronic hyperuricemia is left untreated, tophi (MSU crystals) may form subcutaneously and within the joints in gout patients, sometimes resulting in joint deformity and even loss of motion in severe cases. Tophi may deposit in the ear, subcutaneous tissues, joints, cartilage and kidneys, in turn compromising renal function. This type of tophi usually forms within 3–42 years after the first gout attack, averaging at 11.6 years.[33] However, this interval has reduced to an average of 5–6 years in recent reports.[34,35] Although chronic tophi may not cause intense pain as in acute flares, they could lead to destruction, deformation or functional impairment of the joint and tissue. Physicians should be mindful of any open wounds or scrapes caused by the tophi, and whether they are complicated with bacterial infection. To avoid infection spread leading to severe complications such as osteomyelitis, necrotizing fasciitis, and sepsis that may ultimately result in amputation or death, patients should be advised not to process these open wounds by themselves and should seek immediate medical attention.[36,37]

7. In 2015, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) Collaboratively Updated the Gout Classification Criteria, Where the Entry Criterion Was Defined as At Least 1 Episode of Swelling, Pain, or Tenderness in a Peripheral Joint or Bursa'. The Sufficient Criterion Was Defined as Presence of MSU Crystals in a Symptomatic Joint or Bursa (i.e., in Synovial Fluid) or Tophus'. If This Sufficient Criterion Is Not Met, Scoring of the Parameters in Clinical, Laboratory and Imaging Domains Are then Computed to Determine Whether the Individual Has Gout. (LoE: 3; GoR: B; Agreement: 9.05 ± 0.74)

The gout classification criteria were updated by ACR and EULAR in 2015,[38] in which the entry criterion was defined as 'at least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa'. Therefore, these classification criteria should not be applied to patients without previous episodes of joint swelling and pain. For patients who previously experienced joint pain and fulfilling the sufficient criterion defined as 'presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus', further scoring is not required. If the aforementioned sufficient criterion is not met (the most frequent situation being the lack of synovial microscopy results), scoring of the parameters in clinical, laboratory and imaging domains are then computed to determine whether the individual has gout. Individuals with a score ≥ 8 are classified as having gout (Table 2).

8. Presence of Phagocytosed MSU Crystals in Synovial Fluids Is the Most Definitive Diagnostic Criterion of Gout. However, Its Presence Varies During the Course of a Gout Attack, Making Microscopy Analysis of Synovial Fluid an Examination with Low Sensitivity But Excellent Specificity. (LoE: 3; GoR: B; Agreement: 9.30 ± 0.71)

To date, the presence of phagocytosed MSU crystals confirmed by microscopy analysis of synovial fluid remains the gold standard for diagnosing gout. However, the presence of MSU crystals varies during the course of a gout attack, making microscopy analysis of synovial fluid a test with low sensitivity but excellent specificity. Therefore, even for patients who received a gout diagnosis based on the scoring system,[38] synovial fluid should be aspirated in subsequent acute attacks to confirm diagnosis and facilitate differential diagnosis. Even if MSU crystals are detected in the polarized light microscopy analysis of synovial fluid, the possibility of concomitant gout and septic arthritis should not be overlooked.[36,37] Hence, when bacterial infection in the joint is suspected, Gram stains and bacterial culture of the synovial fluid should be performed. For these reasons, differential diagnosis of gout sometimes involves close examination of patient history, gout flare history, clinical manifestations, disease course and triggering factors, in combination with clinical experience. While the significance of imaging has increased with the rapidly advancing testing technology, none of the imaging tests alone could confirm the diagnosis of gout. To date, diagnoses should still be made based on the 2015 ACR/EULAR classification criteria (Table 2).

Table 2 American College of Rheumatology – European League Against Rheumatism (ACR–EULAR) Gout Classification Criteria (2015)

Item	Criteria (≥ 8 points: gouty arthritis is very likely)	Score: categories	Score
1	Pattern of joint/bursa involvement during episodes (clinical pattern of involvement)	1: Ankle or midfoot	1
		2: 1st MTP	2
2	How many characteristics during episode(s)? (Erythema overlying joint; can't bear touch or pressure to joint; great difficulty with walking or inability to use joint)	0: No characteristics	0
		1: One characteristics	1
		2: Two characteristics	2
		3: Three characteristics	3
3	How many episodes with the following time-course? (≥ 2 time course symptoms, regardless of anti-inflammatory use: (1) time to maximal pain < 24 h; (2) resolution of symptoms in ≤ 14 days; (3) complete resolution (to baseline level) between symptomatic episodes) (Time course–No. of episodes)	0: No typical episodes	0
		1: One episode	1
		2: Recurrent typical episodes	2
4	Evidence of tophus (draining or chalk-like subcutaneous nodule located in typical locations)	0: Absent	0
		4: Present	4
5	Serum urate (ideally scored when patient not taking urate-lowering treatment and patient was > 4 weeks from an episode. If practical, retest under those conditions. Highest value irrespective of timing should be used)	−4: < 4 mg/dL†	-4
		0: ≥ 4 or < 6 mg/dL	0
		2: ≥ 6 or < 8 mg/dL	2
		3: ≥ 8 or < 10 mg/dL	3
		4: ≥ 10 mg/dL	4
6	Synovial fluid analysis of a symptomatic (ever) joint or bursa	0: Not done	0
		−2: Negative for MSU	-2
7	Imaging ultrasound or DECT: evidence of urate deposition in symptomatic joint/bursa (ultrasound: double-contour sign or DECT: demonstrates urate deposition)	0: Absent or not done	0
		4: present	4
8	X-ray erosion (X-ray of hands or feet with ≥ 1 gout-related joint erosion)	0: Absent or not done	0
		4: Present	4

Step 1 - **Entry criteria**: ≥ 1 episode of swelling, pain, or tenderness in a peripheral joint/bursa
Step 2 - **Sufficient criterion**: Presence of monosodium urate (MSU) crystals in a symptomatic joint, bursa, or tophus. (If yes, diagnosis is positive)
Step 3 - **Classification criteria** (≥ 8 scores required for positive diagnosis)
≥ 8 points: gouty arthritis is very likely. †To convert serum urate mg/dL to mmol/L, multiply by 59.48. Modified from 2015 ACR-EULAR Gout Classification Criteria.[38] MTP, metatarsophalangeal joint; DECT, dual-energy computed tomography; MSU, monosodium urate.

9. If Diagnosis Remains Undetermined, Referral to Rheumatologists Should Be Made for Further Confirmation. (LoE: 3; GoR: B; Agreement: 9.75 ± 0.54)

An arthritis flare in patients with high sUA levels may not necessarily be an episode of gout attack. Around one-third of patients have normal sUA levels during acute flares.[34] Moreover, a broad spectrum of diseases can also cause joint disorders with features of redness, swelling, warmth and pain. In order to make correct judgments and differential diagnosis of gout, detailed history, physical examination, synovial fluid analysis or tissue biopsy, as well as blood biochemistry tests, should be performed.[34,38] The list of differential diagnoses should include cellulitis, palindromic rheumatism, septic arthritis, pseudogout, seronegative spondyloarthropathy, rheumatoid arthritis and degenerative arthritis.

10. Sufficient Patient Education Pertaining to Lifestyle Changes As Well As the Benefits of Medication and Treatment Adherence Should Be Provided. (LoE: 3; GoR: B; Agreement: 9.35 ± 0.73)

Based on disease stage (i.e., acute and chronic), pharmacotherapy of gout can be further classified into two main categories. Since the medications used in the respective stages are largely different, it is imperative for patients to understand when to take a particular drug. For example, when suffering from acute pain, anti-inflammatory painkillers and/or colchicine should be taken, whereas urate-lowering drugs would not be beneficial. Contrarily, urate-lowering drugs should be used during the inter-critical and chronic stages to maintain sUA level < 6.0 mg/dL to prevent recurrent gout attacks,[39–43] and perhaps to elicit gradual resolution of tophi (Fig. 1). It is important to consider that many

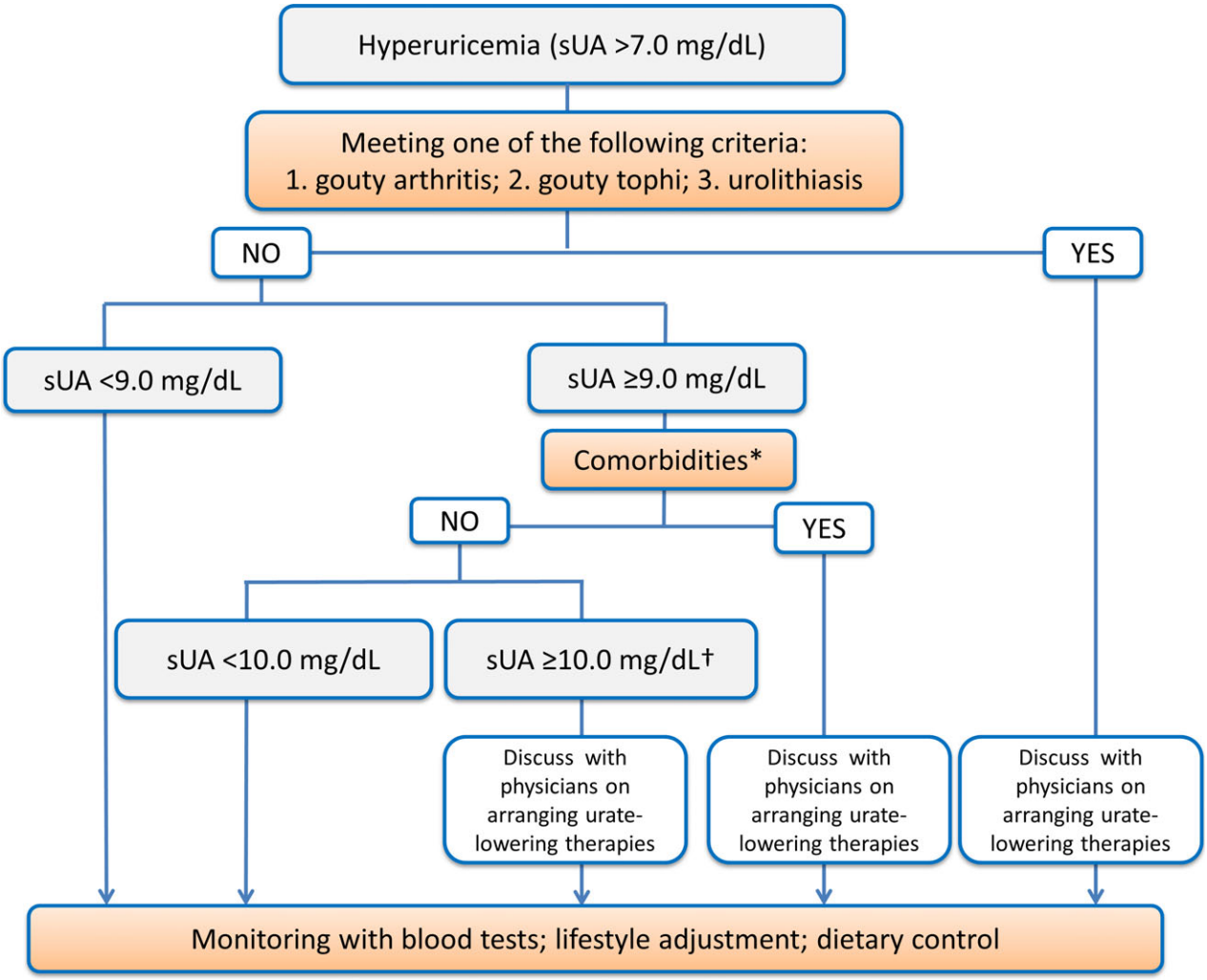

Figure 1 Treatment strategies for gout and hyperuricemia

gout patients are not adequately treated in Taiwan as revealed by the high prevalence of tophi in gout patients[35] and to highlight the burden of gout and hyperuricemia. Thus, we selected the Japanese guideline[41] algorithm as our model. Moreover, ample patient education should be provided in areas such as lifestyle changes, benefits of medication and treatment adherence. Use of unapproved agents/treatments should be prohibited.

11. Acute Gouty Arthritis Generally Resolves Spontaneously Within 1–2 Weeks Without Anti-inflammatory Treatment. Very Few Gout Attacks Extend Over 2 Weeks. Nonetheless, Earlier Use of Anti-inflammatory Painkillers Can Provide Rapid Pain Relief. (LoE: 3; GoR: B; Agreement: 9.00 ± 0.63)

Acute gouty arthritis generally resolves spontaneously within 1–2 weeks without anti-inflammatory treatment and rarely persists over 2 weeks. Nonetheless, earlier use of anti-inflammatory painkillers can provide rapid pain relief.[44] Therefore, upon perceiving signs of pain, the earlier anti-inflammatory painkillers are administered, the better pain-relief response can be delivered, along with the benefits of reduced duration of acute gouty arthritis and medication dosage. Alternatively, applying ice locally may be considered as a supportive measure for pain relief.[45] Depending on comorbidities, three types of anti-inflammatory painkillers are

Table 3 Pharmacotherapeutic options for acute gouty arthritis

Medication	Recommended dosage	Clinical considerations
NSAID	NSAID includes selective and non-selective COX-2 inhibitors. Please refer to package inserts for appropriate dosage	1 During acute flares, earlier use of anti-inflammatory painkillers yields better pain relief response 2 Use with caution in patients with the following conditions: hypertension, cardiovascular diseases, severe renal impairment, peptic ulcer and other comorbidities
Colchicine	1 Colchicine 0.5 mg twice daily in combination with NSAID 2 When indications/premonitions of a flare are perceived, administer colchicine 0.5 mg hourly in the first 3 h, with a total of 3–6 tablets 3 Dosage for geriatric patients (≥ 70 years old) should be halved	1 Taking colchicine > 48 h after an acute arthritis attack is associated with poorer response 2 Dosage for prophylaxis CCr > 50 mL/min: 1# once–twice daily CCr 35–49 mL/min: 1# once daily CCr 10–34 mL/min: 1# 2–3 days Avoid when CCr is < 10 mL/min 3 Adverse events include abdominal pain and diarrhea
Corticosteroid	1 Oral prednisolone 20–30 mg/day 2 Intra-articular corticosteroid injection to a large joint (triamcinolone acetonide 40 mg) 3 Methylprednisolone i.v. 100–150 mg/day for 1–2 days 4 ACTH 40 USP units i.m. or i.v.	Corticosteroid can be an acute/short-term treatment alternative for patients who are ineligible for NSAID and colchicine.

NSAID, nonsteroidal anti-inflammatory drug; COX, cyclooxygenase; CCr, creatinine clearance (mL/min); i.v., intravenous; ACTH, adrenocorticotropic hormone; i.m., intramuscular.

generally prescribed in the treatment of acute gouty arthritis (Table 3). Gout flares are often treated with some combination of steroids, non-steroidal anti-inflammatory drugs (classically, indomethacin), opioids for extreme pain, adrenocorticotropic hormone and colchicine, depending on the patient's age and other risk factors for complications.[34,44] Given that rapid changes in sUA levels may provoke the onset of acute gouty arthritis, introduction or discontinuation of urate-lowering agents is ill-advised during an acute gout attack.

12. The Recommended Goal of Urate-Lowering Therapy Is to Maintain sUA Level < 6.0 mg/dL. For Patients with Tophi, the Preliminary Goal Can Target to Lowering sUA Level to < 5.0 mg/dL to Promote Tophi Dissolution. Liver and Renal Function, As Well As Other Background Factors Should Be Carefully Weighted Prior to Selecting and Administering the Most Appropriate Urate-Lowering Agents. long-Term/Lifelong Urate-Lowering Therapy Is Generally Recommended. (LoE: 3; GoR: B; Agreement: 9.30 ± 0.56)

Currently, gout patients with hyperuricemia are primarily managed by pharmacotherapeutic agents. However, the consensus on when to initiate long-term urate-lowering treatment as a lifelong prophylaxis remains lacking.[41–43,46–48] To prevent acute arthritis attacks and complications, numerous experts have suggested that pharmacotherapeutic treatment should be started earlier,[41] and patients with hyperuricemia and previous episodes of acute gouty arthritis should receive long-term urate-lowering treatment. Long-term/lifelong urate-lowering therapy is generally recommended, even after the cessation of acute arthritis attacks. The goal of urate-lowering therapy should be set to maintain sUA levels < 6.0 mg/dL.[39–43,46,49] Surgical intervention should be reserved for cases where the tophus causes joint destruction/deformity, severe pain, nerve compression, (increased risk of) infection or joint motion restriction.[50,51] For patients with tophi, the initial goal can be set at lowering sUA to < 5.0 mg/dL to promote tophi dissolution.[39–43,46,49]

Urate-lowering drugs can be primarily classified into two types, that is xanthine oxidase inhibitors (XOI) and uricosuric agents. The former group includes allopurinol and febuxostat,[52] whereas the latter includes benzbromarone and sulfinpyrazone (Table 4). While XOI is the first choice in Western countries, allopurinol could cause severe hypersensitivity reactions in Taiwanese patients.[53] Therefore,

prior to selecting and administering urate-lowering drugs, liver and renal functions, as well as other background factors should all be considered. Since uricosuric agents only increase uric acid excretion and do not affect uric acid production, they are not indicated for the following conditions: (i) hyperuricemia caused by uric acid overproduction; (ii) patients with renal insufficiency, as uricosuric agents offer limited efficacy in this circumstance (e.g., avoid prescribing sulfinpyrazone when creatinine clearance [CCr] is < 30 mL/min); and (iii) urolithiasis with uric acid composition, as there is an increased risk of urolithiasis and uric acid nephropathy.[39] To prevent uric acid urolithiasis, uricosuric agents should be started at a lower dose, together with sufficient water intake.

Allopurinol (100, 300 mg/tablet)

This is a XOI that disrupts the purine catabolism, thereby lowering both serum and urinary uric acid concentrations. Allopurinol is generally prescribed for preventing gout attack, nephrolithiasis, and chemotherapy-induced hyperuricemia. Common side effects of allopurinol include rash and gastrointestinal (GI) discomfort. The half-life of allopurinol and its major metabolite oxypurinol is 1–3 h and 17–40 h, respectively. Consequently, allopurinol can be taken once daily. Allopurinol dose adjustment should be based on the patient's renal function (i.e., CCr). Considering that allopurinol is effective in treating both uric acid overproduction and underexcretion, it is frequently prescribed in urate-lowering therapies. Allopurinol is generally very well-tolerated with low incidence of side effects. However, allopurinol hypersensitivity syndrome (AHS) can progress from mild rash to severe hypersensitivity reactions, including skin and mucosal necrosis, Stevens–Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis and renal impairment. The onset of severe cutaneous adverse reactions (SCARs)/severe hypersensitivity largely varies, ranging from 1–728 days (47 days in average) after administration, contributing to a 20–25% mortality rate. Renal insufficiency and age (> 60 years old) appear to be two major factors associated with SCARs. One Taiwanese study published in 2015 retrospectively analyzed the NHI research database and found that the AHS incidence, hospitalization and mortality rate associated with AHS among new users was 0.468%, 0.202% and 0.039%, respectively. Moreover, patients with renal or cardiovascular diseases had an even higher AHS incidence and related mortality rate.[53] Thus, despite that allopurinol is indicated in the following indications/subgroups, it should be used with caution: (i) gouty tophi; (ii) uric acid overproduction (uric acid excretion > 800 mg/24 h under regular diet); (iii) patients who are poor candidates for uricosuric drugs, for example intolerance, renal dysfunction or drug inefficacy; (iv) history of uric acid urolithiasis; (v) cancer patients undergoing chemotherapy (in risk of acute hyperuricemia-induced renal diseases).[39] For patients with normal renal function, the recommended starting dose is 100 mg/day. If no allergic reaction is observed after 1 month of treatment, dose escalation can be considered. The maximum dose is 800 mg/day, and the regular dose is 300 mg/day. Since oxypurinol may accumulate in the kidneys, dose adjustment should be based on renal function for patients with renal dysfunction. The use of allopurinol in human leukocyte antigen (HLA)-B*5801 allele carriers is associated with increased risk of SCARs. Considering that the implementation of prospective HLA-B*5801 genotyping combined with alternative treatment plans has been shown to help lower the risk of SCARs,[54] physicians may perform HLA-B*5801 genotyping prior to prescribing allopurinol. Nevertheless, SCARs can occur in HLA-B*5801 negative patients. Therefore, allopurinol should be used with caution, irrespective of the patient's HLA-B*5801 status. Caution should be exercised when combining allopurinol with other drugs as there may be increased risk of AHS. For example, combination use of allopurinol with ampicillin, thiazide-like diuretics, or angiotensin-converting-enzyme inhibitors may be a risk factor for AHS. Patients allergic to allopurinol may be referred to rheumatologists for further evaluation and treatment. Warfarin users should beware of bleeding. Furthermore, allopurinol dosage should be reduced when used in combination with azathioprine or mercaptopurine.

Febuxostat (80 mg/film-coated tablet)

Different from allopurinol in chemical structure, febuxostat is a non-purine XOI, and thus does not affect the enzyme activities involved in purine or pyrimidine metabolism. Being an XOI, febuxostat is efficacious in treating both overproduction and underexcretion of uric acid.[55] Since febuxostat is mainly excreted by the liver, dose adjustment is not necessary for patients with mild to moderate renal impairment. The Taiwan Ministry of Health and Welfare has approved the use of febuxostat in patients with mild to moderate liver and renal impairment without dose adjustment. The starting dose is 40 mg daily, and can be increased to 80 mg

Table 4 List of urate-lowering agents

Medication	Allopurinol	Febuxostat	Benzbromarone	Sulfinpyrazone
Form	100 mg/tablet	80 mg/tablet	50, 100 mg/tablet, capsule	100 mg/tablet, capsule
Half-life	• Allopurinol: 1–3 h • Oxypurinol (allopurinol metabolite): 17–40 h	5–8 h	12–18 h	1–3 h
Starting dose	100 mg once daily	40 mg once daily	50 mg once daily	100 mg twice daily
Usual dose	300 mg/day	40–80 mg/day	50 mg/day	300–400 mg/day
Maximal dose	800 mg/day	80 mg/day	100 mg/day	800 mg/day
Side effects	Severe allopurinol hypersensitivity syndrome (AHS), rash, dyspepsia	GI discomfort, headache, liver function abnormalities	Liver toxicity, allergy, GI discomfort, liver function abnormalities, urolithiasis	GI discomfort, rash, marrow depression, liver function abnormalities, urolithiasis
Drug interaction	Azathioprine, mercaptopurine, **warfarin**, ampicillin, thiazide diuretics, ACEI	Azathioprine, mercaptopurine	**Warfarin**, salicylate, sulfinpyrazone, etacrynate, pyrazinamide, allopurinol	**Warfarin**, sulfonamides (e.g., sulfadiazine and sulfisoxazole), blood glucose-lowering sulfonylureas, insulin, salicylic acid
Contraindications	Patients with an allergic history to allopurinol	Patients concurrently on azathioprine or mercaptopurine	1. Individuals allergic to benzbromarone 2. Severe hepatic impairment 3. Severe renal impairment 4. Patients with uric acid nephrolithiasis 5. Women who are or may become pregnant	1. Active peptic ulcer 2. Individuals allergic to sulfinpyrazone or other pyrazoles 3. Severe hepatic impairment 4. Severe renal impairment 5. Patients with uric acid nephrolithiasis
Caution	• Adjust dosage based on renal function (i.e., CCr) • Severity of AHS ranges from mild rash to severe hypersensitivity, including skin and mucosal necrosis, Stevens–Johnson syndrome, toxic epidermal necrolysis, hepatic necrosis, and renal impairment • Patients with renal and cardiovascular diseases have higher incidences of severe hypersensitivity and severe hypersensitivity-related mortality • Given that severe hypersensitivity may occur irrespective of the HLA-B*5801 status, physicians are advised to start allopurinol at a low dose and with caution	• Observe signs of cardiovascular disease and monitor liver function • Different from allopurinol in structure, severe skin allergic reactions have scarcely been reported	• Ministry of Health and Welfare in Taiwan requested manufacturer to add the risk of hepatic impairment in warnings. Regular liver function tests should be performed in the first 6 months of treatment. Patients should immediately discontinue benzbromarone and consult their physician upon the onset of hepatic adverse events such as anorexia and general malaise • Patients with renal impairment or urolithiasis should avoid using benzbromarone, if possible	• May inhibit the metabolism of blood glucose-lowering sulfonylureas, causing hypoglycemia • May have inhibitory effects on platelets. Warfarin users should beware of bleeding events • Should not be combined with salicylic acid

GI, gastrointestinal; ACEI, angiotensin-converting-enzyme inhibitor; CCr, creatinine clearance.

after 2 weeks. Continual dose escalation to a maximum of 120 mg/day can be considered if the treatment goal of sUA < 6.0 mg/dL is not met. (Note: the febuxostat prescribing information approved in Taiwan recommends a starting dose of 40 mg once daily. For patients who do not achieve a sUA level < 6.0 mg/dL after 2 weeks with 40 mg once daily, 80 mg once daily is recommended.) A cost-effectiveness study showed that febuxostat can help more patients maintain a sUA level < 6.0 mg/dL compared with allopurinol, and in turn reduces the risk of gout attack and CKD, and thus may be a preferred option especially for patients with CKD stages 3/4.[56] Moreover, febuxostat has been listed as an available choice for patients with urolithiasis in Taiwan' NHI policy since 2016. The rate of side effects with febuxostat is generally low, and the common side effects are GI symptoms (e.g., nausea, vomiting, diarrhea, abdominal pain). Less common side effects are liver function abnormalities, headache and arthralgia. Physicians should observe signs of cardiovascular disease and monitor liver function. Given that febuxostat is structurally different from allopurinol, reports of febuxostat-related SCARs are extremely rare in published studies.

Benzbromarone (50, 100 mg/tablet or capsule)
Benzbromarone is taken orally once daily, usually at the dose of 50 mg/day. The maximum daily dosage should not exceed 100 mg. Use of benzbromarone should be avoided when CCr falls below 20 mL/min for its lack of efficacy. In view of the few cases of fulminant hepatitis reported worldwide,[57] Taiwan Ministry of Health and Welfare has requested a warning about hepatotoxicity to be added to the product labeling, as well as periodic liver function tests in the first 6 months of treatment. Patients should be advised to interrupt treatment and seek immediate medical attention upon the occurrence of symptoms indicative of hepatic adverse event (e.g., anorexia and generalized malaise). However, serious hepatitis has not yet been reported in Taiwan. Moreover, uricosuric agents are relatively contraindicated in patients with urolithiasis. 42 Uric acid clearance at baseline may help select suitable candidates for uricosuric treatment. To avoid uricosuric-induced urolithiasis, proper urinary tract management including adequate fluid intake and, if necessary, urine alkalinization should be instituted.

Sulfinpyrazone (100 mg/tablet or capsule)
This is a uricosuric agent that also possesses antiplatelet effects. The starting dose of sulfinpyrazone is usually 50–100 mg twice daily via oral administration. The common daily dose is 300–400 mg and may increase up to 800 mg in 2–3 divided doses. Side effects include GI discomfort, rash and uric acid urolithiasis. Although adverse events of anemia, leukopenia, thrombocytopenia and agranulocytosis have been rare, routine complete blood count tests for patients receiving sulfinpyrazone are recommended. Sulfinpyrazone may inhibit metabolism of sulfonylurea drugs, leading to hypoglycemia. Individuals concomitantly taking warfarin should observe signs of bleeding, as sulfinpyrazone may have inhibitory effects on platelets.

13. Dietary Control Can Only Lower sUA Levels by Roughly 1.0 mg/dL and Generally Cannot Help Reduce sUA Levels to < 6.0 mg/dL. Therefore, Urate-Lowering Agents Are Needed to Effectively Lower sUA Levels for the Majority of Patients. Dosage of Urate-Lowering Drugs Can Be Reduced If Low-Purine Diet Is Combined. (LoE: 3; GoR: B; Agreement: 8.80 ± 0.93)

Research has suggested that dietary management can only lower sUA level by roughly 1.0 mg/dL.[58] Hence, medication is needed to effectively lower sUA levels for the majority of patients. Medication dosage may be reduced if low-purine diet is integrated as part of the daily diet. The purine contents of fruits, vegetables and dairy products, as well as starch (e.g., grains and potato) are relatively low.[59] The intake of seaweed, protein (e.g., internal organs), and seafood should be limited for their relatively high purine content. Sea cucumber and jellyfish are the few low-purine seafood choices that gout patients may consume. While fat and oil do not affect sUA levels, they may

Table 5 Impacts of food on gout and asymptomatic hyperuricemia patients[59,60]

Risk increased	Risk lowered or unchanged
Meat	Vitamin C, cherries, fruits in general
Seafood	Coffee
Beer and liquor	Milk, yogurt, low-fat dairy products, skim milk powder
High fructose drinks or foods	Carrots, mushrooms, peas, beans, lentils, spinach, broccoli
	Oatmeal
	Vegetarian meat
	Bean products
	Tea, unsweetened/sugar-free soda — no risk
	Red wine

Table 6 Consensus statement of 14 recommendations for the treatment of gout

Item	Description	LoE	GoR	Agreement
1	Hyperuricemia is a major risk factor for gout	3	B	9.80 ± 0.40
2	Gout or hyperuricemia is clearly associated with a variety of comorbidities, including cardiovascular diseases, chronic kidney disease, urolithiasis, metabolic syndrome, diabetes mellitus, thyroid dysfunction, and psoriasis	3	B	9.25 ± 0.62
3	The physiochemical definition of hyperuricemia is a fasting sUA level > 6.8 mg/dL for both adult males and females	3	B	8.40 ± 2.06
4	Immediate urate-lowering therapy is not required for asymptomatic hyperuricemia. Potential causes of hyperuricemia should be identified and properly managed, especially in cases where metabolic syndrome-associated diseases may potentially increase cardiovascular risks	3	B	8.80 ± 1.25
5	The initial phase of an acute gouty arthritis often involves a single joint, and the main clinical manifestations are characterized by intense joint pain, redness, swelling, warmth and pain in the joint and surrounding soft tissues. Fever and arthritis attack in multiple joints may occur in later phases	3	B	8.85 ± 1.06
6	If chronic hyperuricemia is left untreated, tophi (MSU crystals) may form subcutaneously and within the joints of gout patients, sometimes resulting in joint deformity and even loss of motion in severe cases	3	B	9.25 ± 0.83
7	In 2015, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) collaboratively updated the gout classification criteria, where the entry criterion was defined as 'at least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa'. The sufficient criterion was defined as 'presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus'. If this sufficient criterion is not met, scoring of the parameters in clinical, laboratory and imaging domains are then computed to determine whether the individual has gout	3	B	9.05 ± 0.74
8	Presence of phagocytosed MSU crystals in synovial fluids is the most definitive diagnostic criterion of gout. However, its presence varies during the course of a gout attack, making microscopy analysis of synovial fluid an examination with low sensitivity but excellent specificity	3	B	9.30 ± 0.71
9	If diagnosis remains undetermined, referral to rheumatologists should be made for further confirmation	3	B	9.75 ± 0.54
10	Sufficient patient education pertaining to lifestyle changes as well as the benefits of medication and treatment adherence should be provided	3	B	9.35 ± 0.73
11	Acute gouty arthritis generally resolves spontaneously within 1–2 weeks without anti-inflammatory treatment. Very few gout attacks extend over 2 weeks. Nonetheless, earlier use of anti-inflammatory painkillers can provide rapid pain relief	3	B	9.00 ± 0.63
12	The recommended goal of urate-lowering therapy is to maintain sUA levels < 6.0 mg/dL. For patients with tophi, the preliminary goal can target to lowering sUA levels to < 5.0 mg/dL to promote tophi dissolution. Liver and renal function, as well as other background factors should be carefully weighted prior to selecting and administering the most fitting urate-lowering agents. Long-term/lifelong urate-lowering therapy is generally recommended	3	B	9.30 ± 0.56
13	Dietary control can only lower sUA levels by roughly 1.0 mg/dL and generally cannot help reduce sUA levels to < 6.0 mg/dL. Therefore, urate-lowering agents are needed to effectively lower the sUA level for the majority of patients. Dosage of urate-lowering drugs can be reduced if low-purine diet is combined	3	B	8.80 ± 0.93
14	Lifestyle and dietary recommendations for gout patients: maintain healthy weight and waistline, increase physical activity to a moderate level, stay hydrated, and avoid alcoholic and sweetened beverages, as well as animal-derived high purine foods such as internal organs and seafood	3	B	9.10 ± 0.77

LoE: The level of evidence (LOE) and grade of recommendation (GOR) were scored using the Oxford Centre for Evidence-based Medicine Level of Evidence (Oxford Centre for Evidence-Based Medicine: levels of evidence, 2011).[5] [Accessed 10 March, 2016]. Available from URL: http://www.cebm.net/index.aspx?o=5653. Agreement relates to the entire statement for each recommendation and was voted on a scale from 0 to 10 (0, completely disagree; 10, fully agree). sUA, serum uric acid; MSU, monosodium urate.

raise levels of free fatty acids and result in acute gouty attack. Soy bean products generally do not have a high-purine content and thus have little or no effect on sUA levels. In summary, gout patients should avoid consuming high-purine foods such as animal internal organs, seafood and alcohol, especially beer. Moderate consumption of beans and peas has been shown to be safe among gout patients, unless they have previously provoked gout attacks in the individual.

14. Lifestyle and dietary recommendations for gout patients

- Maintain healthy weight and waistline
- Increase physical activity to a moderate level
- Stay hydrated
- Avoid alcoholic and sweetened beverages, as well as animal-derived high purine foods such as internal organs and seafood (Table 5).[39,60] (LoE: 3; GoR: B; Agreement: 9.10 ± 0.77)

Aggressive weight loss measures such as fasting may cause massive cell disruption and subsequent uric acid production, thereby triggering gout flares. Therefore, gradual weight loss at the rate of 1 kg/month is appropriate for overweight patients. As a significant correlation between increased physical activity and reduced mortality in hyperuricemic patients has been demonstrated, patients should be advised to exercise moderately and effectively.[61] Dehydration may provoke gout flares;[30,62,63] nonetheless, sUA level can usually be restored to normal ranges within 3–4 days with proper rehydration.[64] Maintaining hydration is a key measure in preventing gout attacks, acute gout flares induced by antineoplastic chemotherapy, or MSU crystal formation.[64] Table 6 summarizes the consensus statement of 14 recommendations for the treatment of gout.

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AUTHOR CONTRIBUTION

KY wrote the first draft of the present guideline manuscript. All authors contributed to this work and approved the final version.

COMPETING INTERESTS

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REFERENCES

1 Kuo CF, Grainge MJ, Zhang W *et al.* (2015) Global epidemiology of gout: prevalence, incidence and risk factors. *Nat Rev Rheumatol* **11**, 649–62.
2 Kuo CF, Grainge MJ, See LC *et al.* (2015) Epidemiology and management of gout in Taiwan: a nationwide population study. *Arthritis Res Ther* **17**, 13.
3 Chuang SY, Lee SC, Hsieh YT, Pan WH (2011) Trends in hyperuricemia and gout prevalence: Nutrition and Health Survey in Taiwan from 1993–1996 to 2005–2008. *Asia Pac J Clin Nutr* **20**, 301–8.
4 Kuo CF, Grainge MJ, See LC *et al.* (2015) Familial aggregation of gout and relative genetic and environmental contributions: a nationwide population study in Taiwan. *Ann Rheum Dis* **74**, 369–74.
5 Howick J, Chalmers I, Glasziou P *et al.* (2011) OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653
6 Campion EW, Glynn RJ, DeLabry LO (1987) Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. *Am J Med* **82**, 421–6.
7 Annemans L, Spaepen E, Gaskin M *et al.* (2008) Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000–2005. *Ann Rheum Dis* **67**, 960–6.
8 Bieber JD, Terkeltaub RA (2004) Gout: on the brink of novel therapeutic options for an ancient disease. *Arthritis Rheum* **50**, 2400–14.
9 Roubenoff R (1990) Gout and hyperuricemia. *Rheum Dis Clin North Am* **16**, 539–50.
10 Tian Y, Chen K, Xie Z *et al.* (2015) The association between serum uric acid levels, metabolic syndrome and cardiovascular disease in middle aged and elderly Chinese: results from the DYSlipidemia International Study. *BMC Cardiovasc Disord* **15**, 66.
11 Chao TF, Liu CJ, Chen SJ *et al.* (2014) Hyperuricemia and the risk of ischemic stroke in patients with atrial fibrillation–could it refine clinical risk stratification in AF? *Int J Cardiol* **170**, 344–9.
12 Abbott RD, Brand FN, Kannel WB *et al.* (1988) Gout and coronary heart disease: the Framingham Study. *J Clin Epidemiol* **41**, 237–42.
13 Choi HK, Curhan G (2007) Independent impact of gout on mortality and risk for coronary heart disease. *Circulation* **116**, 894–900.

14 Huang CC, Huang PH, Chen JH *et al.* (2015) An independent risk of gout on the development of deep vein thrombosis and pulmonary embolism: a nationwide, population-based cohort study. *Medicine (Baltimore)* **94**, e2140.
15 Chen YF, Lin HH, Lu CC *et al.* (2015) Gout and a subsequent increased risk of erectile dysfunction in men aged 64 and under: a nationwide cohort study in Taiwan. *J Rheumatol* **42**, 1898–905.
16 Roughley MJ, Belcher J, Mallen CD *et al.* (2015) Gout and risk of chronic kidney disease and nephrolithiasis: meta-analysis of observational studies. *Arthritis Res Ther* **17**, 90.
17 Liu P, Chen Y, Wang B *et al.* (2015) Allopurinol treatment improves renal function in patients with type 2 diabetes and asymptomatic hyperuricemia: 3-year randomized parallel-controlled study. *Clin Endocrinol (Oxf)* **83**, 475–82.
18 Sircar D, Chatterjee S, Waikhom R *et al.* (2015) Efficacy of febuxostat for slowing the GFR decline in patients with CKD and asymptomatic hyperuricemia: a 6-month, double-blind, randomized, placebo-controlled trial. *Am J Kidney Dis* **66**, 945–50.
19 Prasad Sah OS, Qing YX (2015) Associations between hyperuricemia and chronic kidney disease: a review. *Nephrourol Mon* **7**, e27233.
20 Juraschek SP, Kovell LC, Miller ER III *et al.* (2013) Association of kidney disease with prevalent gout in the United States in 1988–1994 and 2007–2010. *Semin Arthritis Rheum* **42**, 551–61.
21 Liu WC, Hung CC, Chen SC *et al.* (2012) Association of hyperuricemia with renal outcomes, cardiovascular disease, and mortality. *Clin J Am Soc Nephrol* **7**, 541–8.
22 Chen JH, Pan WH, Hsu CC *et al.* (2013) Impact of obesity and hypertriglyceridemia on gout development with or without hyperuricemia: a prospective study. *Arthritis Care Res (Hoboken)* **65**, 133–40.
23 Wei CY, Sun CC, Wei JC *et al.* (2015) Association between hyperuricemia and metabolic syndrome: an epidemiological study of a labor force population in Taiwan. *Biomed Res Int* **2015**, 369179.
24 Kushiyama A, Tanaka K, Hara S *et al.* (2014) Linking uric acid metabolism to diabetic complications. *World J Diabetes* **5**, 787–95.
25 See LC, Kuo CF, Yu KH *et al.* (2014) Hyperthyroid and hypothyroid status was strongly associated with gout and weakly associated with hyperuricaemia. *PLoS ONE* **9**, e114579.
26 Lai YC, Yew YW (2016) Psoriasis and uric acid: a population-based cross-sectional study. *Clin Exp Dermatol* **41**, 260–6.
27 Burns CM, Wortmann RL (2012). Disorders of purine and pyramidine metabolism. In: Longo FADL, Kasper DL, Hauser SL, Jameson JL, Loscalzo J (eds) *Harrison's Principles of Internal Medicine*. McGraw-Hill, New York.
28 Khanna D, Fitzgerald JD, Khanna PP *et al.* (2012) 2012 American College of Rheumatology Guidelines for Management of Gout Part I: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res* **64**, 1431–46.
29 Vitart V, Rudan I, Hayward C *et al.* (2008) SLC2A9 is a newly identified urate transporter influencing serum urate concentration, urate excretion and gout. *Nat Genet* **40**, 437–42.
30 Choi HK, Atkinson K, Karlson EW *et al.* (2005) Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. *Arch Intern Med* **165**, 742–8.
31 Lin KC, Lin HY, Chou P (2000) The interaction between uric acid level and other risk factors on the development of gout among asymptomatic hyperuricemic men in a prospective study. *J Rheumatol* **27**, 1501–5.
32 Lin HY, Rocher LL, McQuillan MA *et al.* (1989) Cyclosporine-induced hyperuricemia and gout. *N Engl J Med* **321**, 287–92.
33 Yu TF (1984) Diversity of clinical features in gouty arthritis. *Semin Arthritis Rheum* **13**, 360–8.
34 Yu KH, Wu YJJ (2006) Gout and hyperuricemia: recent advances and a systematic review. *Formosan J Rheumatol* **20**, 6–18.
35 Yu KH, Luo SF (2003) Younger age of onset of gout In Taiwan. *Rheumatology* **42**, 166–70.
36 Yu KH, Ho HH, Chen JY *et al.* (2004) Gout complicated with necrotizing fasciitis–report of 15 cases. *Rheumatology (Oxford)* **43**, 518–21.
37 Yu KH, Luo SF, Liou LB *et al.* (2003) Concomitant septic and gouty arthritis–an analysis of 30 cases. *Rheumatology (Oxford)* **42**, 1062–6.
38 Neogi T, Jansen TL, Dalbeth N *et al.* (2015) 2015 Gout Classification Criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheumatol* **67**, 2557–68.
39 Chen DY, Lee IT, Lin SC *et al.* (2016) Taiwan guideline for the management of gout and hyperuricemia – updated 2106. *Formosan J Rheumatol* **30**, 1–32.
40 Hui M, Carr A, Cameron S *et al.* (2017) The British Society for Rheumatology Guideline for the Management of Gout. *Rheumatology* **56**, e1–20.
41 Yamanaka H, Japanese Society of Gout and Nucleic Acid Metabolism (2011) Japanese guideline for the management of hyperuricemia and gout. *Nucleosides Nucleotides Nucleic Acids* **30**, 1018–29.
42 Zhang W, Doherty M, Bardin T *et al.* (2006) 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 (ESCISIT). *Ann Rheum Dis* **65**, 1312–24.
43 Graf SW, Whittle SL, Wechalekar MD *et al.* (2015) Australian and New Zealand recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion in the 3e Initiative. *Int J Rheum Dis* **18**, 341–51.

44 Khanna PP, Gladue HS, Singh MK *et al.* (2014) Treatment of acute gout: a systematic review. *Semin Arthritis Rheum* **44**, 31–8.
45 Schlesinger N, Detry MA, Holland BK *et al.* (2002) Local ice therapy during bouts of acute gouty arthritis. *J Rheumatol* **29**, 331–4.
46 Becker MA, Jolly M (2005). Clinical gout and the pathogenesis of hyperuricemia. In: Koopman WJ (ed) *Arthritis and Allied Conditions*, 15th edn, pp 2303–39. Williams & Wilkins, Baltimore.
47 Chen SY, Chen CL, Shen ML *et al.* (2003) Trends in the manifestations of gout in Taiwan. *Rheumatology (Oxford)* **42**, 1529–33.
48 Ferraz MB, O'Brien B (1995) A cost effectiveness analysis of urate lowering drugs in nontophaceous recurrent gouty arthritis. *J Rheumatol* **22**, 908–14.
49 Wortmann RL, Kelley WN (2005). Gout and hyperuricemia. In: Kelley WN, Ruddy S, Sledge CB (eds) *Kelley's Textbook of Rheumatology*, pp 1402–48. W.B. Saunders, Philadelphia.
50 Falidas E, Rallis E, Bournia VK *et al.* (2011) Multiarticular chronic tophaceous gout with severe and multiple ulcerations: a case report. *J Med Case Rep* **5**, 397.
51 Mittag F, Wuenschel M (2011) Giant gouty tophi of the hand and wrist. *Orthopedics* **34**, e790–2.
52 Becker MA, Schumacher HR Jr, Wortmann RL *et al.* (2005) Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med* **353**, 2450–61.
53 Yang CY, Chen CH, Deng ST *et al.* (2015) Allopurinol use and risk of fatal hypersensitivity reactions: a nationwide population-based study in Taiwan. *JAMA Intern Med* **175**, 1550–7.
54 Ko TM, Tsai CY, Chen SY *et al.* (2015) Use of HLA-B*58:01 genotyping to prevent allopurinol induced severe cutaneous adverse reactions in Taiwan: national prospective cohort study. *BMJ* **351**, h4848.
55 Goldfarb DS, MacDonald PA, Hunt B *et al.* (2011) Febuxostat in gout: serum urate response in uric acid overproducers and underexcretors. *J Rheumatol* **38**, 1385–9.
56 Smolen LJ, Gahn JC, Mitri G *et al.* (2016) Febuxostat in the management of gout: a cost-effectiveness analysis. *J Med Econ* **19**, 265–76.
57 Arai M, Yokosuka O, Fujiwara K *et al.* (2002) Fulminant hepatic failure associated with benzbromarone treatment: a case report. *J Gastroenterol Hepatol* **17**, 625–6.
58 Burns CM, Wortmann RL (2012) Latest evidence on gout management: what the clinician needs to know. *Ther Adv Chronic Dis* **3**, 271–86.
59 Ho WT (1986) Analysis of purines and pyrimidines contents of foods commonly consumed in Taiwan. *J Chinese Nutrit Soc* **11**, 41–62.
60 Torralba KD, De Jesus E, Rachabattula S (2012) The interplay between diet, urate transporters and the risk for gout and hyperuricemia: current and future directions. *Int J Rheum Dis* **15**, 499–506.
61 Chen JH, Wen CP, Wu SB *et al.* (2015) Attenuating the mortality risk of high serum uric acid: the role of physical activity underused. *Ann Rheum Dis* **74**, 2034–42.
62 Choi HK, Curhan G (2005) Adiposity, hypertension, diuretic use and risk of incident gout in women: The Nurses Health Study. *Arthritis Rheum* **52** (Suppl. 9), S733.
63 Feinstein EI, Quion-Verde H, Kaptein EM *et al.* (1984) Severe hyperuricemia in patients with volume depletion. *Am J Nephrol* **4**, 77–80.
64 Schlesinger N (2005) Dietary factors and hyperuricaemia. *Curr Pharm Des* **11**, 4133–8.