Chinese Multidisciplinary Expert Consensus on the Diagnosis and Treatment of Hyperuricemia and Related Diseases

Multidisciplinary Expert Task Force on Hyperuricemia and Related Diseases

Introduction

The prevalence of hyperuricemia (HUA) has increased in China in the recent years in relation to socioeconomic developments and changing lifestyles and diets, with a trend toward onset at younger age. HUA has become the second most common metabolic disease after diabetes mellitus. Like gout, HUA is also associated with the occurrence and progression of disorders of the urinary, endocrine, metabolic, cardio-cerebrovascular, and other systems. Different expert panels have developed guidelines and consensuses on HUA and gout in their respective fields. This consensus has been formulated in accordance with a systematic medical model by a task force including rheumatologists, nephrologists, endocrinologists, cardiologists, neurologists, urologists, and experts in traditional Chinese medicine. It is the first multidisciplinary expert consensus on HUA and its related diseases in China and is aimed at promoting a multidisciplinary collaboration and providing guidelines for best clinical practices.

Definition of Hyperuricemia

According to epidemiological data, HUA has previously been defined as a fasting serum urate level >420 μmol/L in males and >360 μmol/L in females measured on two separate days after a normal purine diet. The saturation level of urate is 420 μmol/L (regardless of sex) in blood, so greater serum urate values can cause precipitation of urate crystals, thus resulting in their deposition in joint cavities and other tissues. Therefore, HUA is defined herein as a serum urate level >420 μmol/L (7 mg/dl).

Epidemiology of Hyperuricemia

The serum urate level is affected by age, sex, race, heredity, food habits, drugs, environment, and other factors. A nationwide epidemiological survey of HUA is still lacking in China. The data from different regions at various times have shown an overall increasing prevalence of HUA in the recent years.[1,2] Epidemiological studies have shown that the prevalence of HUA varies greatly among geographical regions in China over the previous 10 years, ranging from 5.46% to 19.30%, specifically 9.2–26.2% in males and 0.7–10.5% in females.[3-7] The prevalence of gout varies from 0.86% to 2.20% among geographical regions in China, specifically 1.42–3.58% in males and 0.28–0.90% in females.[1,3,8] The prevalence of both HUA and gout increases with age and is more prevalent in males than that in females, in cities than that in rural areas, and in coastal than that in inland areas.[9]

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Pathophysiology of Hyperuricemia-related Systemic Impairment

Uric acid is produced in the liver from purine compounds, which may originate from dietary intake or from the breakdown of body cells [Supplementary Figure 1].[10] Approximately 2/3rd of all uric acid is excreted via the kidneys, and the rest is excreted through the digestive tract. Uric acid undergoes glomerular filtration and renal proximal tubular reabsorption, secretion, and postsecretion reabsorption. The unabsorbed portions are excreted in the urine [Supplementary Figure 2].[11,12] The production and excretion of uric acid are balanced under normal circumstances, but factors that cause overproduction or underexcretion of uric acid can lead to HUA [Supplementary Material 1].[10]

When the serum urate level exceeds its saturation concentration, the precipitated urate crystals directly attach to and deposit in joints and soft tissues around the joints, renal tubules, blood vessels, and other sites, thus resulting in the chemotaxis of neutrophils and macrophages. The interaction between these cells and the crystals leads to the release of pro-inflammatory factors (interleukin [IL]-1β, IL-6, etc.), metalloproteinase 9, hydrolase, and other enzymes,[13-15] which can cause acute and chronic inflammatory injuries of the articular cartilage, bone, kidney, vascular intima, and other tissues.[16]

The damage to multiple organs caused by HUA, involving the heart, brain, and kidneys, may be due to complex mechanisms, such as increased generation of oxygen-free radicals, which damage vascular endothelial cells,[17-21] and upregulation of endothelin and downregulation of nitric oxide synthase expression, thus resulting in vasomotor dysfunction. These phenomena lead to the oxidative modification of low-density lipoprotein cholesterol and subsequent atherosclerosis,[22] which damages mitochondria and lysosomes[23] and results in apoptosis of renal tubular epithelial cells and cardiomyocytes. In addition, the renin–angiotensin–aldosterone system is activated, thereby causing vascular remodeling and organ damage,[16,24] and the inflammatory response is stimulated, thus resulting in platelet aggregation and adhesion.[25,26]

Diagnosis of Hyperuricemia and Gout

Hyperuricemia

A diagnosis of HUA is established when fasting serum urate levels exceed 420 μmol/L after consumption of a normal daily diet on two separate days. Hematological malignancies, chronic renal failure, congenital metabolic abnormalities, poisoning, some drugs, and other factors can elevate serum urate level [Supplementary Materials 1 and 2]. HUA patients younger than 25 years or with a family history of gout must be screened for hereditary purine metabolism abnormalities.

Gout

Gout is defined as the deposition of urate crystals in HUA patients, resulting in arthritis (gouty arthritis), uric acid nephropathy, and kidney stones. Some authors consider only gouty arthritis to be gout.

The possibility of gout should be considered when a HUA patient experiences an acute attack involving a red, tender, hot, and swollen joint, usually the metatarsophalangeal joint of the first toe, ankle, knee, and other joints. In chronic recurrent attacks of gout, patients may manifest with affection of the upper limb joints and the formation of tophi. According to the course of disease, gout is divided into four phases: (1) asymptomatic HUA, (2) acute attack of gouty arthritis, (3) intercritical gouty arthritis, and (4) chronic gouty arthritis.[27]

Key points for gout diagnosis

1. Gouty arthritis: This condition is more common in young and middle-aged men. The initial onset of gouty arthritis is often in the first metatarsophalangeal joint, ankle, midfoot, or knee. It develops abruptly and peaks within 24 h. Usually, only one joint is initially affected. The initial attack may last for several days to several weeks and then resolve completely and spontaneously. Recurrent attacks affect an increasing number of joints and are associated with a longer duration of symptoms and a shorter interval between episodes of arthritis
2. Tophi: Twenty years after the first onset of symptoms, approximately 70% of untreated patients develop tophi, which are often found at the metatarsophalangeal joint of the first toe, the auricle, the extensor side of the forearm, the finger joints, and the elbow. A tophus can be as small as a sesame seed or even larger than an egg. When a tophus is extruded, ulceration or fistula may be formed with a white bean curd-like discharge
3. Synovial fluid examination: Through polarized light microscopy, birefringent needle-shaped sodium urate crystals can be observed in symptomatic synovial fluid, which is valuable for a definite diagnosis
4. Type-B ultrasonic scan: The typical intra-articular "snow storm sign" and "double-contour sign" are valuable for diagnosis. Intra-articular hyperechoic spots and a mass with acoustic shadows are common images indicative of tophi[28]
5. Dual-energy computed tomography (DECT): This technique can reveal the specific distinction between tissues and periarticular urate crystals, which is useful for diagnosis[29,30]
6. X-ray: Swollen soft tissue can be observed in early acute arthritis. Recurrent attacks may destroy articular cartilage edges, irregular articular surfaces, and stenosis of the joint space on X-ray films. Patients with tophaceous deposits may have punched-out osteolytic lesions with a sharp edge. The lesions appear as a semicircle or continuous arc. Bone hyperplasia reactions can be observed on the bony edge.

In the past, gout was usually diagnosed in accordance with the gout classification criteria released by the American College of Rheumatology (ACR) in 1977 [Supplementary Material 3]. If any three items are satisfied,

the condition can be classified as gout.[31] In the recent years, both ultrasonic and DECT have been used widely to examine the joints. Adopting the gout classification criteria proposed by the ACR/European League against Rheumatism in 2015 is recommended (a web-based calculator can be accessed at http://goutclassificationcalculator.auckland.ac.nz, and through the ACR and European League against Rheumatism websites). A threshold score ≥8 classifies an individual as having gout. Current studies have shown that the 2015 classification criteria are more scientific, comprehensive, and systematic, with significantly improved sensitivity for the diagnosis of gout than previous criteria.[32-35]

Complications

Gouty arthritis is the most common manifestation in patients with gout; however, chronic HUA can cause or aggravate the damage to multiple organs, which may be complicated by renal disease (acute urate nephropathy, chronic urate nephropathy, and nephrolithiasis), hyperglycemia, dyslipidemia, hypertension, coronary heart disease, cardiac insufficiency, and stroke.[36]

PROPHYLAXIS AND TREATMENT OF HYPERURICEMIA

After a diagnosis of HUA and gout is established, patient education and lifestyle interventions should be instituted immediately. Comprehensive and long-term management is required for HUA patients. The patients should be stratified and managed when pharmacologic treatment is initiated, and the appropriate treatment target should be set according to the serum urate level and concomitant clinical symptoms and/or signs.

Patient management

Patient management is the basis of the prevention and treatment of HUA and gout, and it should be focused on long-term management. For patients, it is the scientific approach to fully understand the health hazards of the disease, form, and carry out the regimen of treatment with the help of physicians. Patients should be referred to a high-level medical institution promptly when they have severe complications or comorbidities or experiences of unsatisfactory treatment effects.[37]

Management for hyperuricemic patients

(1) Improve awareness of HUA and relevant knowledge. (2) Provide health guidance regarding diet, exercise, and other aspects and individualized lifestyle interventions. (3) Screen for and prevent gout and complications. (4) Cooperate with specialists to develop multidisciplinary treatment regimens for comorbidities and avoid the use of urate-elevating drugs as much as possible [Supplementary Material 2]. (5) In addition to lifestyle intervention, patients with drug therapy must maintain long-term target control of serum uric acid levels.

Management for patients with gout

(1) Patients with gouty arthritis must follow the principles of HUA management. (2) Physicians should inform patients to avoid possible risk and inducing factors in daily life, propose correct preventive measures, and design an individualized emergency treatment protocol for acute attacks. (3) The initiation of pharmacologic urate-lowering therapy (ULT) should be considered after relief of acute attacks of gout. The established pharmacologic ULT should be continued without interruption during an acute attack. Medicines for preventing acute attacks of gout should be given to the patients during their initial pharmacologic ULT.

Management for patients with complications

(1) Patients should be screened for complications or comorbidities and administered a multidisciplinary combination therapy regimen immediately after a diagnosis of HUA or gout. (2) Drugs with nephrotoxic potential must be avoided in patients with acute or chronic urate nephropathy, renal function must be monitored to guide the selection of drugs, and glucocorticoids may be used as the first choice treatment during the acute phase of gout for patients with moderate-to-severe renal insufficiency. (3) The urine must be alkalized in patients with nephrolithiasis, and stone-dissolving therapy or surgery should be provided if necessary. (4) Hypoglycemic, lipid-lowering, and antihypertensive treatments should be given actively to patients with comorbidities of hyperglycemia, dyslipidemia, and hypertension, for which it would be better to use a drug that facilitates excretion of uric acid. (5) Cyclooxygenase (COX)-2 inhibitors should be avoided during an acute attack of gouty arthritis in patients with myocardial infarction or cardiac dysfunction.

Management for high-risk population

High-risk populations include individuals with a first-degree relative with HUA or gout, individuals with an unhealthy sedentary lifestyle and a purine-rich or high-fat diet, and individuals with obesity, metabolic abnormalities (e.g., abnormal glucose tolerance or diabetes, dyslipidemia, and nonalcoholic fatty liver), cardio-cerebrovascular diseases (e.g., hypertension, coronary heart disease, heart failure, and stroke), or chronic kidney disease [Supplementary Material 4 for definition and staging]. A regular screening program should be established for these high-risk populations. Education should be emphasized to disseminate the knowledge of HUA and gout and improve the awareness of HUA prophylaxis and treatment. Serum urate levels should be monitored regularly to identify and manage HUA or gout as early as possible.

Nonpharmacological treatments

Encouraging a balanced diet, limiting total daily caloric intake, and controlling purine content in the diet are recommended. A low purine diet is encouraged [Table 1], but the intake of animal offal, seafood, meat, and other purine-rich foods should be strictly limited. Purine-rich vegetables (such as lettuce, spinach, mushrooms, and cauliflower), beans, and bean products are not significantly associated with HUA and gout attacks. Patients are encouraged to consume more fresh vegetables and appropriately consume beans and bean products (patients with renal insufficiency must consume such foods under the guidance of a specialist).[38]

Table 1: Dietary recommendations for hyperuricemic patients

Diet recommendation	Food type
Encourage	Vegetables; low-fat and nonfat milk and milk products; eggs
Limit	Beef, lamb, pork, and purine-rich sea food; table sugar, desserts, table salt (including sauces and gravies), red wine, and fruit wine
Avoid	High-fructose beverages; animal offal; yellow rice wine, beer, and spirits

Drinking large amounts of water can shorten the duration of a gout attack and relieve symptoms. Adequate body water should be maintained for patients with normal heart and kidney functions by frequently drinking water to maintain a daily urine output of 2000–3000 ml. Milk and dairy products (especially nonfat milk and low-calorie yogurt) can be consumed. The consumption of cola, orange juice, apple juice, and other fructose-containing beverages and sugar-containing soft drinks should be avoided. The relationship between coffee and HUA and gout is inconclusive. Studies have shown that drinking coffee does not increase the risk of HUA but may decrease the risk of gout.[39,40]

Fruits are rich in potassium and Vitamin C, which can decrease the risk of gout attacks.[41] HUA patients can consume fruits with low fructose contents, such as cherries, strawberries, pineapple, watermelons, and peaches.

Alcohol intake can increase the risk of gout attacks in HUA patients,[42] and there is a dose–response relationship between alcohol intake and the risk of gout onset.[43] Alcohol intake should be limited, and yellow rice wine, beer, and spirits should be avoided by HUA patients. Whether the consumption of red wine can increase serum uric acid levels remains controversial.[44,45]

Obesity can increase the risk of gout in HUA patients.[46] Weight loss can effectively decrease serum urate levels.[47,48] It is recommended that HUA patients should keep their body weight within a normal range (body mass index: 18.5–23.9 kg/m^2).

Regular physical activity can decrease the number of gout attacks and the HUA-related mortality.[49] HUA patients should be encouraged to adhere to appropriate exercise programs. Moderate aerobic exercise for at least 150 min every week is recommended (30 min/d, 5 d/week) to keep the heart rate within the range ([220 − age] × [50–70%]) during exercise. Strenuous activity or suddenly becoming cold should be avoided because both might trigger gout attacks.

Smoking and passive smoking increase the risk of HUA and gout. Smoking should be ceased, and passive smoking should be avoided.

Pharmacologic treatments
Pharmacologic treatments should be adopted to address HUA when the effect of nonpharmacological intervention is poor. The treatment regimen should be individualized and stratified, and treat-to-target therapy should be adopted; moreover, the regimen should be appropriate for long-term management. The dose should be titrated gradually. Excessive fluctuations of serum urate levels over a short duration might induce an acute attack of gout, which should be avoided.

Urate-lowering therapies
The commonly used urate-lowering agents in clinical practice include two classes: urate production inhibitors and uricosuric agents. The pharmacologic ULT should be selected according to the cause of disease, comorbidities, and hepatic and renal functions. The principles of pharmacologic treatments are shown in Table 2.[37,50,51]

Urate production inhibitors
Xanthine oxidase inhibitor decreases the synthesis of uric acid by inhibiting the activity of xanthine oxidase. Commonly used drugs include allopurinol and febuxostat.

Allopurinol
In adults, the starting dose is 50–100 mg/d. The serum urate level should be monitored every 2–5 weeks. The dose can be increased by 50–100 mg increments to a maximum dose of 600 mg/d in patients if the serum uric acid target is not reached. The starting dose should not exceed 1.5 mg/estimated glomerular filtration rate (eGFR) per day in patients with renal insufficiency,[52] and the recommended dose is 50–100 mg/d for GFR categories G3–G4. Allopurinol is contraindicated in patients with GFR category G5. Allopurinol can cause skin allergic reactions and hepatic and renal injury. Fatal exfoliative dermatitis and other hypersensitivity syndromes might develop in severe cases. Human leukocyte antigen (HLA)-B*5801 allele positivity, usage of thiazide diuretics, and renal insufficiency are risk factors for the development of adverse reactions to allopurinol. The prevalence of the HLA-B*5801 allele in Korean and Thai populations of Han Chinese is significantly higher than that in Caucasian. Screening for this gene has been before initiating allopurinol treatment.[50,53] Allopurinol is contraindicated in HLA-B*5801 allele-positive patients.

Febuxostat
This drug is a novel selective inhibitor of xanthine oxidase. The initial dose is 20–40 mg/d, which can be titrated gradually to a maximum of 80 mg/d if the serum uric acid target is not reached after 2–5 weeks. Febuxostat has a better safety profile in patients with renal insufficiency and renal transplantation because it is cleared mainly via the liver. No dose adjustment is needed in patients with mild-to-moderate renal insufficiency (GFR categories G1-3). However, this drug should be used with caution in patients with severe renal insufficiency (GFR categories G4–G5). Adverse reactions to febuxostat include hepatic impairment, nausea, and rash.[54,55]

Uricosuric drugs
Benzbromarone increases urinary excretion of uric acid and therefore lowers serum urate levels by suppressing

Clinical manifestations	Timing of ULT initiation	Therapeutic target
(1) ≥2 attacks of gouty arthritis or (2) one attack of gouty arthritis concomitant with any of the following: age <40 years, evidence of tophi or urate deposition in the joint cavity, uric acid nephrolithiasis or renal impairment (GFR categories ≥ G2), hypertension, impaired glucose tolerance or diabetes mellitus, dyslipidemia, obesity, coronary heart disease, stroke, or cardiac insufficiency	Start of treatment	SUA <360 μmol/L; SUA <300 μmol/L in patients with tophi, chronic gouty arthritis, or frequent attacks of gouty arthritis; decrease in SUA to below 180 μmol/L is not recommended
(1) one attack of gouty arthritis or (2) no gout attack but having any of the following: uric acid nephrolithiasis or renal impairment (GFR categories ≥ G2), hypertension, impaired glucose tolerance or diabetes mellitus, dyslipidemia, obesity, coronary heart disease, stroke, or cardiac insufficiency	SUA >480 μmol/L	The same as above
None	SUA >540 μmol/L	SUA <420 μmol/L; decrease in SUA to below 180 μmol/L is not recommended

Renal impairment (GFR categories G2) is defined as an eGFR of 60–89 ml·min^{-1}·1.73 m^{-2}. Frequent attacks of gouty arthritis indicate an occurrence of two or more episodes per year. GFR: Glomerular filtration rate; eGFR: Estimated glomerular filtration rate; SUA: Serum uric acid; ULT: Urate-lowering therapy.

renal tubular reabsorption of uric acid by inhibiting urate transporter 1 (URAT1).

Benzbromarone

The starting dose of benzbromarone is 25–50 mg/d in adults taken orally after breakfast, which should be adjusted to 75 mg/d or 100 mg/d 2–5 weeks later, according to the serum urate level. Benzbromarone can be used in patients with mild-to-moderate renal dysfunction or renal transplantation. The recommended dose is 50 mg/d in patients with an eGFR of 20–60 ml·min^{-1}·1.73 m^{-2}.[56-58] Benzbromarone is contraindicated in patients with an eGFR <20 ml·min^{-1}·1.73 m^{-2} or uric acid nephrolithiasis. Urine must be alkalized in patients taking benzbromarone to adjust the urine pH to 6.2–6.9. The daily urine output should be maintained above 2000 ml in patients with normal heart and renal functions. Adverse reactions of benzbromarone include gastrointestinal discomfort, diarrhea, rash, and hepatic impairment.[59,60]

Novel urate-lowering drugs

These drugs include uricases and selective uric acid reabsorption inhibitors.

Uricases

Uricases are enzymes, including rasburicase and pegloticase, which decompose uric acid into soluble products for excretion. Rasburicase is a recombinant urate oxidase that is used primarily for the prevention and treatment of acute HUA in patients with hematological malignancies, especially HUA caused by radiochemotherapy. Rasburicase can induce antibody production and thereby decrease its efficacy.[61] Pegloticase is an apegylated recombinant urate oxidase that is indicated for the majority of refractory gout. It can be used in adult patients with refractory gout for whom other drugs are ineffective or contraindicated. The main adverse reactions associated with pegloticase include serious cardiovascular events and infusion and immunogenic reactions.[62]

Selective uric acid reabsorption inhibitors

RDEA594 (lesinurad) acts by inhibiting URAT1 and the organic anion transporter 4. It is indicated for gout patients who are unable to achieve the target serum urate level with a xanthine oxidase inhibitor alone at an adequate dose. It can also be used in combination with a xanthine oxidase inhibitor. Hydration should be increased during lesinurad treatment, and renal function should be assessed before the initiation of lesinurad treatment. Lesinurad is not recommended for patients with GFR categories G3b-5.[63]

Urine alkalization

This treatment is recommended to maintain urine pH of 6.2–6.9 in patients receiving urate-lowering drugs, especially uricosuric drugs, and in patients with uric acid nephrolithiasis to increase the solubility of uric acid in urine. A high urine pH might increase the risk of calcium phosphate, calcium carbonate, and other stone formation.

Sodium bicarbonate

This treatment is indicated for patients with chronic renal insufficiency and concomitant HUA and/or gout. The starting dose is 0.5–1g, orally, three times daily. Sodium bicarbonate should be given in an interval of 1–2 h with other drugs. The main adverse reactions include flatulence and gastrointestinal discomfort. Attention should be paid to sodium overload and hypertension in patients who are treated for a long time.

Citrate preparations

These preparations include potassium sodium hydrogen citrate, potassium citrate, and sodium citrate. Potassium sodium hydrogen citrate is the most commonly used preparation. Citrate is the strongest endogenous inhibitor of stone formation in urine, and it alkalizes the urine, thereby increasing the solubility of uric acid, dissolving uric acid stones, and preventing the formation of new stones. The starting dose of potassium sodium hydrogen citrate is 2.5–5.0 g/d. Urine pH should be monitored to adjust its dose accordingly. Potassium sodium hydrogen citrate is contraindicated in patients with acute renal injury or chronic

renal failure (GFR categories G4–G5), severe acid–base disorder, or hepatic insufficiency.[64]

Pharmacologic therapy for acute gout attacks

The goal of treatment for an acute attack is to quickly control the symptoms of arthritis. Bed rest is required for patients during an acute attack. The affected limb should be raised, and a local cold compress can be applied. Drugs should be administered as soon as possible to control the acute attack. The earlier the therapy is initiated, the better the efficacy. Colchicine or nonsteroidal anti-inflammatory drugs (NSAIDs) are the first-line options for the treatment of acute arthritis attacks. If patients have contraindications or respond poorly to these drugs, corticosteroids are an option for controlling inflammation. For patients with one or two large joints involved, an intra-articular injection of short-acting corticosteroids can be considered when they respond poorly to systemic treatment. However, repeated injections over the short term should be avoided.

Colchicine

Colchicine exerts its analgesic effect by inhibiting the chemotaxis and phagocytosis of leukocytes and mitigating inflammatory reactions. Colchicine is recommended to be administered as soon as possible (within 12 h) after the onset of a gout attack. The treatment effect is significantly decreased if treatment is initiated 36 h after the onset. The initial loading dose is 1.0 mg, and this is followed by 0.5 mg 1 h later and then by 0.5 mg 12 h later, 1–3 times daily. Colchicine should be avoided in patients receiving cytochrome P_{450} 3A4 or phosphorylated glycoprotein inhibitors (such as cyclosporine A, clarithromycin, verapamil, and ketoconazole). Adverse reactions related to colchicine increase with the dosage. Common adverse reactions include nausea, vomiting, diarrhea, abdominal pain, and other gastrointestinal effects. Colchicine should be discontinued immediately if adverse reaction symptoms are observed. Abnormal liver function and elevated transaminases might be observed in a few patients. Colchicine should be discontinued if the liver function test value exceeds two times the upper limit of normal. Hematuria, oliguria, and abnormal renal function suggest renal impairment in patients. In such cases, the dosage of colchicine should be decreased accordingly. The maximum dosage is 0.5 mg daily in patients with an eGFR 35–49 ml·min⁻¹·1.73 m⁻² and 0.5 mg once every other day in patients with an eGFR 10–34 ml·min⁻¹·1.73 m⁻². Colchicine is contraindicated with an eGFR <10 ml·min⁻¹·1.73 m⁻² or when the patient is on dialysis. Colchicine can cause bone marrow suppression, and routine blood tests should be performed for monitoring during treatment.

Nonsteroidal anti-inflammatory drugs

NSAIDs include nonselective COX and COX-2 inhibitors. Full-dose treatment with fast-acting NSAIDs is recommended at an early stage if there are no contraindications. The main adverse reactions of nonselective COX inhibitors are gastrointestinal ulcer or perforation, upper gastrointestinal bleeding, and other gastrointestinal adverse reactions. If patients are intolerant to nonselective COX inhibitors, COX-2 inhibitors should be considered, which decrease gastrointestinal adverse reactions by 50%. However, all NSAIDs are contraindicated in patients with active gastrointestinal ulcer or bleeding or prior recurrent gastrointestinal ulcer or bleeding.[65] COX-2 inhibitors should be avoided in patients with concomitant myocardial infarction and cardiac insufficiency because they may increase the risk of cardiovascular events. Renal function should be monitored during NSAID treatment. The use of NSAIDs is not recommended in nondialysis patients with severe chronic kidney diseases (GFR categories G4–G5).

Glucocorticoids

These drugs are primarily used for patients with severe acute gout attack and serious systemic symptoms, with contraindications or a poor response to colchicine and NSAIDs, or with renal insufficiency. When administered systemically, oral prednisone is administered at a dosage of 0.5 mg·kg⁻¹·d⁻¹ continuously for 5–10 d, and is then discontinued; alternately, it can be administered at a dosage of 0.5 mg·kg⁻¹·d⁻¹ for 2–5 d, then tapered off until discontinuation, with a total course of 7–10 d.[37,50] Intravenous glucocorticoids might be considered if oral administration is inappropriate. Attention should be paid to the adverse reactions to glucocorticoids, such as hypertension, diabetes mellitus, water and sodium retention, and infections. The use of long-acting glucocorticoids should be avoided. For patients with one or two large joints involved, an intra-articular injection of short-acting corticosteroids can be considered if the patient responds poorly to systemic treatment. However, repeated injections over the short term should be avoided.

Treatment with a new drug

An IL-1 receptor antagonist can be considered for the treatment of refractory acute gout when NSAIDs, colchicine, or corticosteroids are ineffective or when patients have contraindications to these drugs.[37,66,67]

Prevention of acute attacks of gout during initial urate-lowering therapy

Acute attacks of gout are easily induced by fluctuations in serum urate levels. Patients with gout should receive prophylaxis to prevent gout attacks during the first 3–6 months of ULT. Oral low-dose colchicine is preferred. The recommended dosage is 0.5–1 mg/d. No dose adjustment is needed for patients with mild renal insufficiency, but renal function should be monitored regularly. The dosage should be decreased by half, 0.5 mg orally once every other day, or tapered as appropriate for patients with moderate renal insufficiency. The use of colchicine should be avoided in patients with severe renal insufficiency or who are on dialysis. NSAIDs can be used when colchicine is ineffective, but attention should be paid to the occurrence of adverse reactions such as those related to the gastrointestinal tract and cardiovascular system as well as renal impairment. NSAIDs should be used with caution in patients with coronary heart disease and other chronic cardiovascular diseases. Alternatively,

low-dose prednisone or prednisolone (≤10 mg/d) can be used when patients respond poorly or have contraindications to colchicine and NSAIDs. In such cases, osteoporosis and other adverse reactions should be monitored and prevented. The prophylactic treatment should be maintained for 3–6 months and tailored as appropriate depending on the attack of gouty arthritis.[37,50]

Prophylactic drugs are not recommended for HUA patients without prior gout attack who are receiving ULT, but they should be informed of the risk of gout attacks. Treatment should be administered in a timely manner after the occurrence of acute gouty arthritis. Subsequent prophylactic medications should also be considered.

Treatment for tophi

Tophi can be gradually dissolved and decreased in size after active ULT to maintain the serum urate level below 300 μmol/L for more than 6 months. Surgical treatments can be considered for larger tophi associated with nerve compression or tophaceous ulceration or for those patients who cannot be cured after prolonged treatment. However, the patients still require a standardized comprehensive treatment.[37,50]

Traditional Chinese medicine

Traditional Chinese medicine interventions for this disease emphasize the principles of simultaneous recuperation, combination treatment of the disease and symptoms, and management according to the disease stage. Patients should choose foods with caution; abstain from unhealthy choices; avoid drinking alcohol; and avoid overeating fatty, sweet, and greasy foods. They should adopt long-term dietary therapy to correct their constitutional imbalance, such as *Semen Coicis, Semen Euryales*, and *Rhizoma Dioscoreae*. Patients should also enhance their physical fitness and promote mental health via exercises, which are conducive to disease prevention and treatment. For HUA, the basic treatment is to invigorate the spleen, eliminate toxins, and remove blood stasis, which are used throughout the course of treatment regardless of the presence of clinical symptoms. Commonly used medicines include *Semen Coicis, Rhizoma Smilacis Glabrae, Rhizoma Smilacis Chinensis, Rhizoma Dioscoreae Septemlobae*, and *Rhizoma Polygoni Cuspidati*.[68]

If the symptom is related to joints with sudden redness, swelling, and thermalgia, these symptoms are indicative of acute-stage gout with predominant pathogenic excess. In such cases, it is better to adopt the strategy of clearing heat and eliminating dampness, activating meridians, and relieving arthralgia using an agent such as Simiao Powder or Danggui Niantong Decoction. Commonly used medicines include *Cortex Phellodendri, Rhizoma Atractylodis, Semen Plantaginis, Herba Artemisiae Scopariae, Rhizoma et Radix Notopterygii,* and *Feculae Bombycis*. If the pain is recurrent and refractory and is associated with joint deformity or subcutaneous nodules or ulceration, a chronic stage of gout is indicated, the underlying pathology of which is asthenia complicated with sthenia. In such cases, it is appropriate to

resolve phlegm and remove blood stasis, relieve arthralgia and dredge collaterals; this strategy should be combined with fortifying the spleen, invigorating the kidney, and nourishing the liver using, for example, the upper-middle-lower gout recipe. Commonly used medicines include *Radix Clematidis, Rhizoma Arisaematis, Rhizoma Curcumae Longae*, and *Ramulus Cinnamomi*.

Symptoms in the kidney characterized by sandy urine or oliguria and body edema indicate gouty nephropathy. It is appropriate to adopt the strategy of fortifying the spleen, invigorating the kidney, eliminating turbid phlegm, and removing blood stasis. In addition, treatment should be adjusted on the basis of the syndrome differentiation in terms of deficiency excess and cold–heat patterns. In addition to turbid phlegm and blood stasis, excess syndrome is mostly caused by dampness-heat and stone obstruction. Patients with dampness-heat might suffer from frequent and dripping urination with burning pain. They should be treated with medicines to eliminate the heat and promote diuresis, such as Bazhen Decoction or Bixie Huadu Decoction. Commonly used medicines include *Herba Plantaginis, Herba Polygoni Avicularis, Herba Taraxaci, Fructus Chaenomelis*, and *Radix Gentianae Macrophyllae*. Patients with stone obstruction might have dysuria, sudden interruption of urination, or sandy urine. For this symptom, a treatment that relieves stranguria and expels stones, such as Shiwei Powder, is suggested. Commonly used medicines include *Folium Pyrrosiae, Talcum*, and *Spora Lygodii*. Deficiency syndrome is mostly attributed to the spleen and kidney. The patient should be treated using a strategy to warm the yang to resolve fluid retention if the yang deficiency is dominant. The recommended formula is Wenpi Decoction and Jisheng Shenqi Pills. Commonly used medicines include *Radix Astragali, Radix Codonopsis, Cortex Eucommiae, Rhizoma Cibotii, Radix Dipsaci*, and *Radix Aconiti Lateralis Preparata*. For patients with yin deficiency, nourishing yin and enhancing body resistance are the main treatments and include the recommended formulas of Zuogui Pills or Liuwei Dihuang Pills. Commonly used medicines include *Radix Rehmanniae Preparata, Rhizoma Polygonati, Fructus Lycii*, and *Fructus Corni*.

Modern pharmacological studies are useful for choosing the appropriate medicines or formulas in addition to the syndrome identification and treatment based on traditional Chinese medicine. Studies have shown that *Rhizoma Smilacis Glabrae*,[69,70] *Rhizoma Polygoni Cuspidati*,[71] *Rhizoma Smilacis Chinensis*,[72] and *Rhizoma Curcumae Longae*[73] can inhibit xanthine oxidase activity and decrease serum urate levels, whereas *Rhizoma Dioscoreae Septemlobae*,[74] *Fructus Gardeniae*,[75] and *Herba Plantaginis*[76] can regulate uric acid transporter expression, decrease the reabsorption of uric acid, and promote the excretion of uric acid.

In addition, local treatment with traditional Chinese medicine by topical application, steaming, and washing enables medicines to act directly at the lesions and aids in dispersion of swelling and pain relief. Enemas in traditional Chinese

medicines not only achieve detoxification and purge the internal organs but also facilitate the absorption of active ingredients via the intestinal tract, so the medicines can act systemically. Local acupuncture in combination with the stimulation of acupoints along meridian might simultaneously address the symptoms and cause of the disease.

Multidisciplinary diagnosis and treatment

HUA is often associated with comorbidities of other systems, such as metabolic, renal, and cardio-cerebrovascular diseases. A multidisciplinary treatment approach is appropriate for managing HUA patients with such comorbidities.

Hyperuricemia and kidney diseases

The urate deposits in the kidney lead directly to chronic urate nephropathy, acute uric acid nephropathy, and uric acid nephrolithiasis in HUA patients. In contrast, renal diseases also affect the excretion of uric acid and induce secondary HUA. The HUA in turn might lead to or aggravate renal diseases. HUA is an independent risk factor for chronic kidney diseases.

Chronic urate nephropathy

The pathogenesis of chronic urate nephropathy involves the persistent deposition of sodium urate crystals in the interstitial tissue of the renal medulla; these crystals might activate the local renin-angiotensin-aldosterone system; damage endothelial cells; and cause high glomerular pressure, chronic inflammatory reactions, interstitial fibrosis, and other pathological changes.[77] If HUA patients develop renal tubular dysfunction, such as increased nocturia, low specific gravity urine, and low-molecular-weight proteinuria, chronic urate nephropathy is suspected. The increment of serum urate levels might not correspond to the degree of renal impairment. Chronic urate nephropathy can be considered after other chronic kidney diseases are excluded. However, it is usually difficult to differentiate chronic urate nephropathy from other chronic kidney diseases with concomitant HUA. Renal biopsy is often required to verify the deposition of urate crystals in renal tissue to confirm the diagnosis. Late-stage chronic urate nephropathy can lead to a decreased GFR and chronic renal failure.

Nonpharmacological therapy should be initiated immediately after the diagnosis of chronic urate nephropathy is confirmed. Pharmacologic therapy should be administered to patients with poor efficacy on the basis of the serum urate level and comorbidities. ULT should be initiated to treat to a target serum urate level of <360 μmol/L in patients with renal impairment (GFR categories ≥G2) or HUA patients (SUA >480 μmol/L) with uric acid nephrolithiasis. In patients with severe gout (such as tophi, chronic arthritis, and frequent attacks), the serum urate level should be controlled more strictly with a target value <300 μmol/L but lowering the level to <180 μmol/L is not recommended.[37,50,51]

Acute uric acid nephropathy

Acute uric acid nephropathy is acute oliguric or anuric renal failure induced by renal tubular obstruction due to excessive uric acid crystals deposits caused by severe HUA.[78] It is observed primarily in tumor lysis syndrome.[79] Patients with acute uric acid nephropathy can develop urinary tract obstruction, low back pain, and either oliguria or anuria. Acute uric acid nephropathy should be considered when acute renal injury is complicated by a significant increase of serum urate level (>900 μmol/L Renal biopsy is required to confirm the diagnosis, but tubulointerstitial nephritis should be excluded. Renal pathological examination can reveal varying degrees of renal tubular degeneration and necrosis with concomitant partial tubular atrophy and renal interstitial fibrosis. There are no obvious lesions or ischemic shrinkage of the capillary loops in glomeruli. Uric acid crystals deposits can be observed in renal tubular cavities under a polarized light microscope.[80]

Acute uric acid nephropathy is usually reversible. The focus of management is on its prevention. Intravenous hydration should be instituted actively in high-risk patients to maintain a urine output at 80–100 ml·m^{-2}·h^{-1} if the heart and kidney functions are adequate. A recombinant uricase or xanthine oxidase inhibitor is preferred to maintain the serum urate level below 300 μmol/L Emergency management is required for patients with confirmed acute uric acid nephropathy. Timely and effective treatments are expected to recover the renal function to a normal level. The treatment measures are as follows:[81] (1) a strict low purine diet; (2) hydration therapy: daily liquid intake reaching 3000 ml to maintain the urine output at 80–100 ml·m^{-2}·h^{-1} if there are no contraindications; (3) urate-lowering drugs: these drugs should be selected according to the serum urate level or the risk of tumor lysis syndrome before treatment (allopurinol is preferred in patients with serum uric acid <480 μmol/L without severe renal dysfunction, and only a mild-to-moderate risk of tumor lysis syndrome before treatment; uricase is recommended in patients with increased serum urate before treatment; and owing to limited clinical data, febuxostat should be used with caution only in patients who are not able to use uricase and allopurinol); and (4) hemodialysis if necessary.

Uric acid nephrolithiasis

With improved living standards and changing dietary patterns, the incidence of uric acid nephrolithiasis is showing an increasing trend. Urate stones account for 8–14% of the urinary stones in the United States[82] and 5.1% in China,[83] and are second only to calcium oxalate stones. The decrease in solubility and excess saturation of uric acid in urine are the premises of urate stone formation. Low back pain and hematuria are usually characteristic of uric acid nephrolithiasis. When acute obstruction occurs, it is likely to trigger acute kidney injury, with symptoms of fever, oliguria, anuria, hydronephrosis, and elevated serum creatinine, among others. Chronic obstruction may result in hydronephrosis, renal parenchymal atrophy, and even end-stage renal diseases.[84]

The urine pH is often lower than 6.0 in patients with uric acid nephrolithiasis. Urate crystals can be seen on urine sediment examination. Hyperechoic areas with sound shadows can

be seen in type-B ultrasonic examination of the kidney. Uric acid stones are not visible on X-ray films (negative stones). Negative stones should be differentiated from renal xanthine and hypoxanthine stones; the latter two are insoluble in an alkaline environment. However, calculus shadows with varying densities are observed in mixtures with calcium oxalate, calcium phosphate, and other ingredients. Intravenous pyelography can reveal a filling defect. CT is highly useful for the diagnosis of uric acid nephrolithiasis. For uric acid calculus, the CT values often range from 300 to 400 HU, which is lower than that of the cystine calculus but higher than that of blood clots and tumors. The composition of the excreted calculus should be analyzed to confirm the diagnosis.

Uric acid nephrolithiasis can be treated with stone removal therapy, extracorporeal shock wave lithotripsy (ESWL), and/or surgical treatment.

Stone removal therapy

This therapy applies to patients with small stones (diameter of 0.5–1.0 cm) who lack symptoms such as urinary tract obstruction, infection, or pain. Such therapies include general support therapy, traditional Chinese medicine, and litholytic therapy.[85] General support therapy includes increasing fluid intake, avoiding purine-rich foods, and exercising appropriately. Among the commonly used traditional Chinese medicines are Paishi granules (for removing stones) and Niao Shi Tong (for managing urolithiasis). Oral potassium sodium hydrogen citrate granules are usually used in clinical practice as a litholytic therapy.

Shock wave lithotripsy

This procedure is indicated for patients with poor outcomes after stone removal therapy for 1–2 months, such as (1) stones in the renal pelvis, upper and middle calyx (diameter <2.0 cm); (2) small stones in the lower calyx (diameter <1.0 cm) and larger stones in the lower calyx (diameter of 1.0–2.0 cm), which should be assessed according to the presence of adverse factors; and (3) a proportion of staghorn stones (diameter of 2.0–3.0 cm or surface area <500 mm^2). Shock wave lithotripsy is contraindicated in patients with organic obstruction distal to stones, renal insufficiency, or uncontrolled urinary tract infection.

Surgical treatment

Surgical treatment is adopted for conditions in which uric acid calculus has resulted in urinary obstruction, severe infection, or impaired renal functions. It includes open surgery, percutaneous nephrolithotomy, and retrograde intrarenal surgery. For kidney calculus larger than 2.0 cm and complicated kidney calculus, percutaneous nephrolithotomy is recommended. Percutaneous nephrolithotomy is contraindicated in the case of failure to establish percutaneous access to the kidney due to severe body deformity, extreme obesity, and other problems. Retrograde intrarenal surgery can be used to remove stones with a diameter <2.0 cm, which respond poorly to ESWL. For an uncommon uric acid calculus like a staghorn calculus, the combined application of litholysis therapies, ESWL, and percutaneous nephrolithotomy can be adopted.

Chronic kidney disease complications in hyperuricemia

Patients with chronic kidney disease should be treated in the same way as chronic urate nephropathy patients regarding when to initiate therapy and the target value. The drugs used to treat HUA should be selected according to the primary disease, complications, and the state of renal function in patients with chronic kidney disease.

The use of NSAIDs is not recommended during acute attack of gout in patients with chronic kidney disease (GFR categories G4–G5). In such cases, glucocorticoids can be administered orally for a short term or by intra-articular injection. Alternatively, low-dose colchicine can be administered as appropriate according to the eGFR (see "Pharmacologic therapy for acute attacks of gout").[86,87]

ULT can decrease the uric acid load in the glomeruli and delay the progression of chronic kidney disease. The treatment for these patients should be individualized with inhibitors of urate production or uricosuric drugs. Renal impairment may increase the toxicity of allopurinol. Allopurinol treatment should be initiated at a lower dose and carefully titrated upward (see "Pharmacologic treatments").[52,88-91] No dose adjustment is needed for febuxostat in patients with mild-to-moderate renal insufficiency (GFR categories G1–G3) and patients with mild-to-moderate hepatic injury (Child-Pugh class A/B). However, febuxostat should be used with caution in patients with GFR categories G4–G5. The incidence of hypersensitivity syndrome associated with febuxostat is lower than that associated with allopurinol.[54,55] The uricosuric drug benzbromarone can be used in patients with mild-to-moderate renal insufficiency (eGFR: 20–60 ml·min^{-1}·1.73 m^{-2}). The recommended dosage is 50 mg/d. However, benzbromarone is contraindicated in patients with uric acid nephrolithiasis or severe renal insufficiency (eGFR <20 ml·min^{-1}·1.73 m^{-2}).[56-58]

The prophylactic use of colchicine is required in patients with chronic kidney disease during ULT to prevent ULT-induced gout attacks. However, colchicine is contraindicated in patients with an eGFR <0 ml·min^{-1}·1.73 m^{-2} or who are on dialysis, but low-dose corticosteroids can be considered for short-term use.

Hyperuricemia and metabolic syndrome

Metabolic syndrome is a clinical syndrome that is characterized by the coexistence of multiple risk factors for cardiovascular diseases, such as obesity, hypertension, hyperglycemia, and dyslipidemia, in one individual. It is a combination of multiple metabolically interrelated risk factors. These factors directly contribute to the occurrence of atherosclerotic cardiovascular diseases and also increase the risk of type 2 diabetes mellitus.[92] HUA is related to metabolic syndrome closely. Some authors also consider HUA to be one of the components of metabolic syndrome.

Insulin resistance is the common pathophysiological basis for metabolic syndrome.[93-96]

Obesity

Obesity, especially abdominal obesity, is closely related to HUA.[97] Obesity-related mild chronic inflammation and insulin resistance can increase the risk of HUA and gout. Weight loss, especially a decrease in abdominal circumference, is an effective way to decrease serum urate levels via a nonpharmacological approach.[98,99]

Hypertension

A large number of studies have shown that HUA is an independent risk factor for hypertension.[100,101] Antihypertensive drugs other than diuretics are preferred for patients with both HUA and hypertension. Losartan potassium has a uricosuric effect and can decrease cardiovascular events by 13–29% by lowering serum uric acid.[102,103] Amlodipine is a dihydropyridine calcium antagonist with a uricosuric effect. It is recommended for use in hypertensive patients with ischemic stroke.[104]

Hyperglycemia

The prevalence of HUA increases in patients with diabetes mellitus.[105] An elevated serum urate level not only increases the risk of type 2 diabetes mellitus[106] but also serves as an independent risk factor for the future development of type 2 diabetes mellitus in the nondiabetic population.[107,108] HUA is also an important predictor of the progression and aggravation of diabetic nephropathy.[109-112]

Pharmacologic ULT should be initiated immediately in patients with abnormal glucose metabolism if their serum urate level exceeds 480 μmol/L The currently available clinical data do not show that hypoglycemic agents have adverse effects on the serum urate level. Sulfonylureas can promote the excretion of uric acid.[113] The α-glucosidase inhibitor acarbose can decrease the elevated serum urate level caused by the decomposition of sucrose.[114] Thiazolidinediones may decrease the serum urate level by improving insulin resistance.[115,116] Dapagliflozin, canagliflozin, and other sodium glucose co-transporter 2 inhibitors can decrease serum urate levels.[117,118]

Dyslipidemia

Dyslipidemia is a common comorbidity of HUA and gout. Hypertriglyceridemia is an independent predictor of HUA. Atorvastatin is preferred for patients with hypercholesterolemia or atherosclerosis with HUA.[119] Fenofibrate is preferred for patients with hypertriglyceridemia and concomitant HUA.[120] Both atorvastatin and fenofibrate have a uricosuric effect.

Hyperuricemia and cardiovascular disease

HUA is an independent risk factor for cardiovascular disease and simultaneously interacts with many traditional cardiovascular risk factors in contributing to the development, progression, and outcome of cardiovascular diseases.[121,122] Pharmacologic ULT should be initiated in HUA patients with comorbidities such as hypertension, coronary heart disease,

heart failure, and other cardiovascular diseases, when the serum urate level exceeds 480 μmol/L. Such ULT can effectively prevent and treat HUA-related cardiovascular diseases and decrease the incidence of cardiovascular events.[123-127]

In addition to lowering serum uric acid, xanthine oxidase inhibitors can improve endothelial function, decrease oxidative stress, regulate myocardial energy metabolism, and thereby further decrease the incidence of cardiovascular events.[128] NSAIDs are associated with water and sodium retention and renal impairment, both of which might increase the risk of aggravation of heart failure and hospitalization for heart failure. Therefore, the use of such drugs should be avoided as much as possible in patients with acute or chronic heart failure.

Hyperuricemia and hypertension

There is an independent correlation between HUA and hypertension. The serum urate level is an independent predictor of the development of long-term blood pressure changes and the prognosis of hypertension. The risk of hypertension increases by 15–23% for each additional increase of 60 μmol/L in serum uric acid.[129,130] The antihypertensive options for HUA patients with concomitant hypertension are detailed in the section titled "HUA and metabolic syndrome."

Hyperuricemia and coronary heart disease

For each additional increase of 60 μmol/L in serum uric acid, cardiovascular mortality and ischemic heart disease mortality increase by 26% and 30% in women and by 9% and 17% in men, respectively, and the risk of coronary heart disease increases in women by 48%.[101,102] HUA is an independent risk factor for all-cause mortality and coronary heart disease mortality in women. The effects of HUA on the development and prognosis of coronary heart disease differ between men and women, possibly because of the effects of estrogen.[131,132]

The effects of aspirin, atorvastatin, and other drugs on serum uric acid levels should be considered when these agents are used for primary and secondary prevention of coronary heart disease. Aspirin has a dose-specific effect on the metabolism of uric acid: high-dose aspirin (>3 g/d) significantly inhibits the reabsorption of uric acid in renal tubules and promotes the excretion of uric acid. Moderate-dose aspirin (<1–2 g/d) inhibits the excretion of uric acid in renal tubules and thereby increases serum uric acid.[133] Low-dose aspirin (75–325 mg/d) slightly increases serum uric acid.[134] However, considering the cardio-cerebrovascular benefits associated with the antiplatelet effects of using aspirin at 75–325 mg/d, it is not recommended to discontinue aspirin dosages of 75–325 mg/d in patients with concomitant HUA. In such cases, it is recommended to concomitantly alkalize the urine, drink more water, and monitor serum urate levels. Atorvastatin has a weak effect on lowering serum uric acid levels.[119] It is preferred for the secondary prevention of coronary heart disease with concomitant HUA.

HUA is an independent risk factor for contrast-induced acute kidney injury. It is recommended to measure serum

uric acid, stratify the risk, increase hydration, avoid the use of hyperosmotic contrast agents, and decrease the doses of contrast agents when HUA patients undergo coronary CT imaging or coronary angiography.[135]

Hyperuricemia and heart failure

Elevated serum uric acid is associated with the severity of chronic heart failure, which increases with worsening New York Heart Association functional classification. Increased serum uric acid is an independent predictor of poor outcome in patients with chronic heart failure.[126,134]

The use of loop diuretics or complication of chronic renal failure may increase the serum urate level and result in a poor outcome in patients with acute decompensated heart failure. After controlling for these confounders, HUA is still associated with a poor short-term outcome (in-hospital death) and poor long-term prognosis (cardiac death and readmission due to heart failure).[136]

Long-term use of potassium-wasting diuretics (especially thiazide diuretics) might decrease renal clearance of uric acid and thereby induce or aggravate HUA. Nonthiazide diuretics are preferred for heart failure patients with concomitant HUA. Moreover, an adequate amount of water should be consumed, and the urine should be alkalized. In addition, concomitant use of thiazide diuretics and allopurinol should be avoided as much as possible because thiazide diuretics might increase the risk of hypersensitivity reaction to allopurinol.

Hyperuricemia and neurological diseases

HUA is associated with a variety of neurological diseases. HUA contributes to the occurrence and poor prognosis of ischemic stroke, whereas it has protective effects in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. The inherent connection between uric acid and neurological diseases remains to be further investigated.

Hyperuricemia and ischemic stroke

An elevated serum uric acid level, especially above 420 μmol/L is an independent risk factor for stroke.[137] HUA contributes to the occurrence of stroke[138] and is an independent risk factor for ischemic stroke in the Chinese population.[19] In addition, long-term follow-up studies in nonstroke patients have found that an increased serum urate level may be an important serological marker for asymptomatic cerebral infarction and possible stroke in female patients,[139] thus suggesting that controlling the serum urate level may be of greater significance for the prevention of stroke in female HUA patients.

Higher serum urate levels are positively correlated with the risk of early death after stroke. An elevated serum urate level may suggest a poor 90-day outcome after stroke.[140] Increased serum uric acid is an independent risk factor for the recurrence of stroke in stroke patients.[16] Serum urate levels can be used as an indicator to predict the risk of death and recurrence of stroke in patients with acute ischemic stroke.

In patients with cerebral infarction undergoing thrombolysis, higher serum uric acid levels are associated with a smaller cerebral infarction volume and better prognosis (modified Rankin Scale Score <2 points). Lower serum uric acid levels are associated with malignant middle cerebral artery infarction and hemorrhagic transformation.[141] Elevated serum uric acid levels are positively correlated with improved clinical symptoms in patients receiving thrombolysis. Concomitant alteplase for thrombolysis and intravenous infusion of uric acid can improve the prognosis of female patients, but it cannot improve in male patients potentially because the baseline serum uric acid level in women is lower than that in men.[142,143]

Based on the above studies, long-term management of HUA, which lowers serum uric acid levels, might help decrease the occurrence and improve the outcome of ischemic stroke. The initial and final targets of management should refer to relevant sections. It is only recommended for patients with acute ischemic stroke receiving thrombolytic therapy to maintain serum uric acid at higher levels only for a short term, which helps in improving clinical symptoms and outcomes. Pharmacologic therapy should be considered in HUA patients with stroke and a high risk of possible stroke. The effects of aspirin, atorvastatin, and other drugs on serum uric acid should be considered adequately during pharmacologic treatment. Specific details are provided in the relevant section of pharmacologic therapy for coronary heart disease.

Hyperuricemia and neurodegenerative diseases

Alzheimer's disease is the most common type of dementia. The serum uric acid levels in patients with mild cognitive dysfunction and Alzheimer's disease are lower than those in the normal population. A diet high in uric acid can delay the progression of mild cognitive dysfunction to Alzheimer's disease.[144] An elevated serum uric acid level helps to decrease the incidence of Alzheimer's disease and protects cognitive function in patients with Alzheimer's disease.[145,146] A lower serum uric acid level may increase the risk of cognitive impairment in patients with mild cognitive dysfunction.[147]

Parkinson's disease is a common degenerative disease of the central nervous system that occurs in the elderly. The risk of Parkinson's disease is lower in the population with high serum uric acid levels.[148,149] An increased serum uric acid level helps decrease morbidity and delay the progression of Parkinson's disease.[150,151] The risk of developing Parkinson's disease is relatively low in male patients with high serum uric acid levels or gout, but no such correlation has been found in women.[152]

The relationship between the serum urate level and neurological diseases is complex. HUA might contribute to the occurrence and poor prognosis of ischemic stroke, whereas the physiological serum urate level has a certain protective effect on the nervous system. An excessively low serum urate level might increase the risk of developing neurodegenerative diseases. Therefore, it is helpful for

human health to maintain a serum urate level within a reasonable range.

This is the first multidisciplinary expert consensus on HUA and associated diseases. This consensus provides comprehensive insights into the diseases from the perspective of systematic medicine. Experts from various specialties considered the latest results of domestic and foreign research, the actual situation, and the features of clinical diagnosis and treatment practices in China. This consensus was reached through a multidisciplinary collaboration integrating traditional Chinese medicine with Western medicine and both internal medicine and surgical approaches for consistently, comprehensively, and systematically managing HUA and associated diseases. The purpose of these efforts was to improve awareness of HUA and associated diseases in various disciplines in China, to standardize and guide clinical practice, and eventually to improve patient outcomes. This consensus adopts unified diagnostic criteria for HUA and proposes individualized, stratified, and treat-to-target approaches and long-term management. The consensus recommendations also set the lower limit of the ULT target after considering the physiological role of uric acid. This consensus emphasizes the importance of patient management and nonpharmacological therapy. Since relevant research data are lacking in the Chinese population and the quality of clinical studies remains to be improved, this consensus suggests that multidisciplinary joint studies should be performed in the future, especially on the following topics: an epidemiological study of HUA and the influential factors in different regions of China, a prospective ULT study examining the outcome of the corresponding systemic impairment, and a study of the safety and efficacy of pharmacologic ULT monotherapy and combination therapy. These studies should provide a basis for drafting Chinese guidelines on treating HUA and related diseases.

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Supplementary information is linked to the online version of the paper on the Chinese Medical Journal website.

Conflicts of interest
There are no conflicts of interest.

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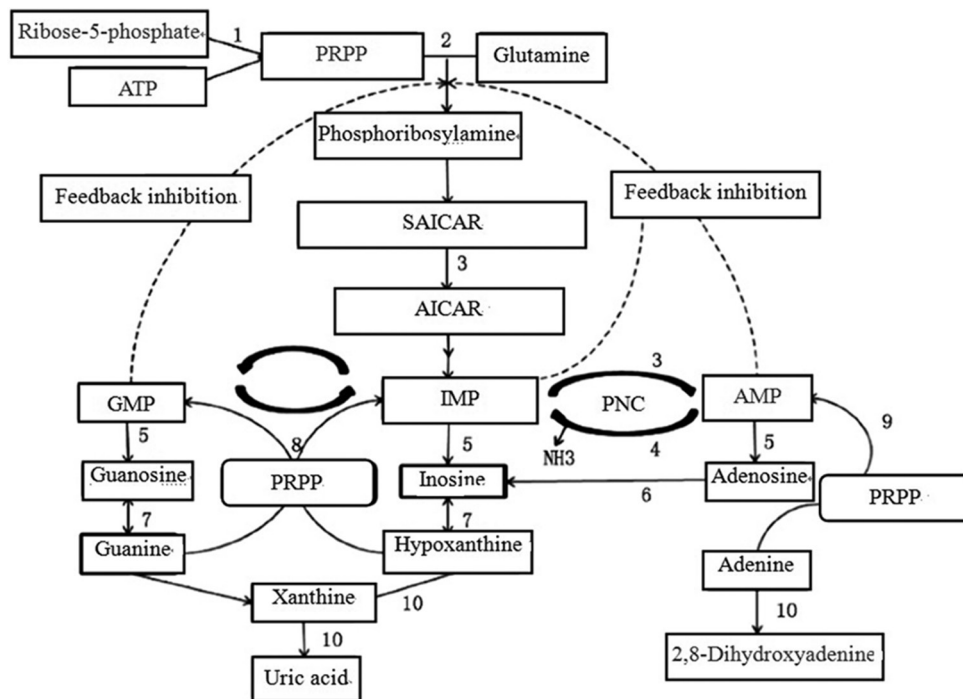
Supplementary Figure 1: Schematic diagram of uric acid production. (1) PRPP synthetase; (2) amidophosphoribosyltransferase; (3) adenylosuccinate lyase; (4) adenylate deaminase; (5) 5-nucleotidase; (6) adenosine deaminase; (7) purine nucleoside phosphorylase; (8) HPRT; (9) APRT; (10) xanthine oxidase. PRPP: Phosphoribosyl pyrophosphate; HPRT: Hypoxanthine phosphoribosyltransferase; APRT: Adenine phosphoribosyltransferase; AICAR: Aminoimidazole carboxamide ribotide; AMP: Adenosine monophosphate; ATP: Adenosine triphosphate; GMP: Guanylate; IMP: Inosine monophosphate; PNC: Purine nucleotide cycle; SAICAR: Succinylaminoimidazole carboxamide ribotide.
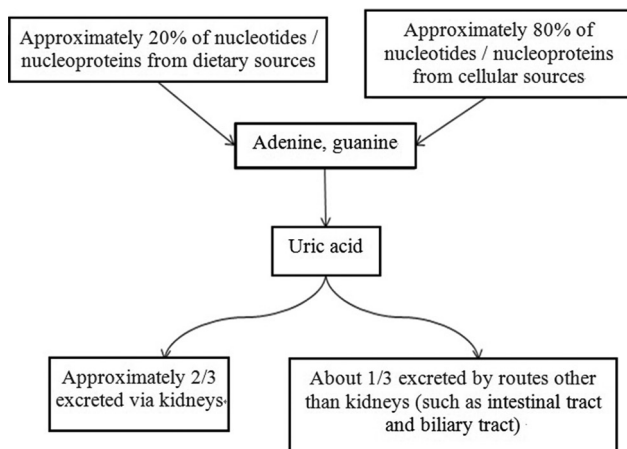
Supplementary Figure 2: Schematic diagram of uric acid metabolism.

SUPPLEMENTARY MATERIALS

Supplementary Material 1: Classification of hyperuricemia by pathophysiology

Urate overproduction

Primary idiopathic, hypoxanthine phosphoribosyltransferase deficiency, phosphoribosyl pyrophosphate synthetase overactivity, hemolytic processes, lymphoproliferative diseases, myeloproliferative diseases, polycythemia vera, psoriasis, Pagetas disease, glycogenosis III, V, and VII, rhabdomyolysis, exercise, alcohol, obesity, purine-rich diet.

Decreased uric acid excretion

Primary idiopathic, renal insufficiency, polycystic kidney disease, diabetes insipidus, hypertension, acidosis, (lactic acidosis, diabetic, ketoacidosis), starvation ketosis, berylliosis, sarcoidosis, lead intoxication, hyperparathyroidism, hypothyroidism, toxemia of pregnancy, Barttercy syndrome, Down syndrome, drug ingestion, salicylates (>2 g/d), diuretics, alcohol, levodopa, ethambutol, pyrazinamide, nicotinic acid, cyclosporine.

Combined mechanism

Glucose-6-phosphatase deficiency, fructose-1-phosphate aldolase deficiency, alcohol, shock.

Supplementary Material 2: Medications affecting uric acid metabolism

Medications with uricosuric activity

Acetohexamide, glyceryl guaiacolate, adrenocorticotrophic hormone, glycopyrrolate, ascorbic acid, halofenate, azauridine, losartan, benzbromarone, meclofenamate, calcitonin, phenolsulfonphthalein, chlorprothixene, phenylbutazone, citrate, probenecid, dicumarol, radiographic contrast agents, diflunisal, salicylates (>2 g/d), estrogens, sulfinpyrazone, fenofibrate, glucocorticoids, zoxazolamine.

Urate-elevating medications

Salicylates (<2 g/d), thiazide diuretic, pyrazinamide, cyclosporine A, cytotoxic drug, levodopa, loop diuretics, ethambutol, tacrolimus, niacin, methoxyflurane.

Supplementary Material 3: The American College of Rheumatology criteria for Acute Arthritis of Primary Gout (1977)

1. The presence of characteristic urate crystals in the joint fluid
2. A tophus proved to contain urate crystals by chemical or polarized light microscopic means
3. Presence of six of the following 12 clinical, laboratory, and X-ray phenomena.

(1) More than one attack of acute arthritis. (2) Maximum inflammation developed within 1 day. (3) Monoarthritis attack. (4) Redness observed over joints. (5) First metatarsophalangeal joint, painful or swollen. (6) Unilateral first metatarsophalangeal joint attack. (7) Unilateral tarsal joint attack. (8) Suspected tophus. (9) Hyperuricemia. (10) Asymmetric swelling within a joint on X-ray. (11) Subcortical cysts without erosions on X-ray. (12) Joint fluid culture negative for organisms during attack.

Supplementary Material 4: Definition and classification of chronic kidney disease

Definition of chronic kidney disease

CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.

Criteria for CKD (either of the following present for >3 months)	
Markers of kidney damage (one or more)	Albuminuria (AER ≥30 mg/24 h; ACR ≥30 mg/g [≥3 mg/mmol])
	Urine sediment abnormalities
	Electrolyte and other abnormalities due to tubular disorders
	Abnormalities detected by histology
	Structural abnormalities detected by imaging
	History of kidney transplantation
Decreased GFR	eGFR <60 ml·min^{-1}·1.73 m^{-2} (GFR categories G3a–G5)

GFR: Glomerular filtration rate; AER: Albumin excretion rate; ACR: Albumin-creatinine ratio; CKD: Chronic kidney disease.

Staging of CKD		
GFR category	GFR (ml·min^{-1}·1.73 m^{-2})	Terms
G1	≥90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

GFR: Glomerular filtration rate; AER: Albumin excretion rate; ACR: Albumin-creatinine ratio; CKD: Chronic kidney disease.

Adult GFR estimating equations (2009 CKD-EPI creatinine equation):

$141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{Age}$ (×1.018 if female), where SCr is serum creatinine (in mg/dl), κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min is the minimum of SCr/κ or 1, and max is the maximum of SCr/κ or 1.

Equations expressed for specified sex and serum creatinine level		
Gender	Serum creatinine	Equation for estimating GFR
Female	≤0.7 mg/dl (≤62 mmol/L)	$144 \times (SCr/0.7)^{-0.329} \times 0.993^{age}$
Female	>0.7 mg/dl (>62 mmol/L)	$144 \times (SCr/0.7)^{-1.209} \times 0.993^{age}$
Male	≤0.9 mg/dl (≤80 mmol/L)	$141 \times (SCr/0.9)^{-0.411} \times 0.993^{age}$
Male	>0.9 mg/dl (>80 mmol/L)	$141 \times (SCr/0.9)^{-1.209} \times 0.993^{age}$

SCr: Serum creatine; GFR: Glomerular filtration rate.