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2024 Update of Chinese Guidelines for Management of Hyperuricemia and Gout Part II: Recommendations for Patients With Common Comorbidities

Changgui Li¹ | Mingshu Sun² | Zhen Liu³ | Detian Li⁴ | Changqian Wang⁵ | Zibin Tian⁶ | Yuxiang Dai⁷ | Zhe Feng⁸ | Chengfu Xu⁹ | Dongbao Zhao¹⁰ | Feng Wei¹¹ | Bo Ban¹² | Chao Xie¹³ | Zhenmei An¹⁴ | Jia Liu¹⁵ | Zhuo Li¹⁶ | Yuwei He³ | Xinde Li³ | Fei Yan³ | Lin Han³ | Lidan Ma³ | Xiaoyu Cheng³ | Tian Liu³ | Xufei Luo¹⁷ | Lingling Cui³ | Ying Gong³ | Can Wang³ | Yaolong Chen¹⁷ | Zhaohui Lyu¹⁸ | Ronald M. L. Yip¹⁹ | Jiajun Zhao²⁰

¹Department of Endocrinology, Xiang'an Hospital of Xiamen University, Xiamen, Fujian, China | ²Department of Rheumatology, Xiang'an Hospital of Xiamen University, Xiamen, Fujian, China | ³Department of Metabolism, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China | ⁴Department of Nephrology, Shengjing Hospital of China Medical University, Shenyang, Liaoning, China | ⁵Department of Cardiology, Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China | ⁶Department of Gastroenterology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China | ⁷Department of Cardiology, Zhongshan Hospital, Fudan University, Shanghai, China | ⁸Department of Nephrology, The First Medical Center of Chinese PLA General Hospital, Beijing, China | ⁹Department of Gastroenterology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, Zhejiang, China | ¹⁰Department of Rheumatology, The First Affiliated Hospital of Naval Medical University (Shanghai Changhai Hospital), Shanghai, China | ¹¹Department of Endocrinology, The First Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, Neimonggu, China | ¹²Department of Endocrinology, Affiliated Hospital of Jining Medical University, Jining, Shandong, China | ¹³Department of Endocrinology and Metabolism, Peking University Third Hospital, Beijing, China | ¹⁴Department of Metabolism, West China Hospital, Sichuan University, Chengdu, China | ¹⁵Department of Endocrinology, Beijing Chao-Yang Hospital, Capital Medical University, Beijing, China | ¹⁶Department of Endocrinology and Metabolism, The First Hospital of Jilin University, Changchun, Jilin, China | ¹⁷Research Unit of Evidence-Based Evaluation and Guidelines, Chinese Academy of Medical Sciences (2021RU017), School of Basic Medical Sciences, Lanzhou University, Lanzhou, Gansu, China | ¹⁸Department of Endocrinology, The First Medical Center of Chinese PLA General Hospital, Beijing, China | ¹⁹Tung Wah Group of Hospitals Integrated Diagnostic and Medical Centre, Kwong Wah Hospital, Kowloon, Hong Kong, China | ²⁰Department of Endocrinology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong, China

Correspondence: Changgui Li (changguili@vip.163.com) | Jiajun Zhao (jjzhao@sdu.edu.cn)

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ABSTRACT

Objective: The aim of this updated guideline is to provide comprehensive recommendations for the management of gout in patients with common comorbidities, such as chronic kidney disease (CKD), cardiovascular disease (CVD), diabetes, osteoarthritis (OA), and gastrointestinal disorders.

Methods: This guideline was developed by a multidisciplinary expert panel consisting of specialists in endocrinology, rheumatology, nephrology, cardiology, gastroenterology, and methodology. The development process adhered to standard methodologies, including PICO (population, intervention, comparator, and outcomes) question deconstruction, systematic literature review, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) for evidence and recommendation evaluation, Delphi voting, and expert consensus.

Changgui Li and Mingshu Sun contributed equally to this work.

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Results: The guideline presents 26 evidence-based recommendations addressing seven clinical questions for patients with hyperuricemia and gout in the context of comorbidities. Key recommendations include the maintenance of strict serum urate targets, particularly for patients with CKD stage ≥ 3 , chronic gouty arthritis, and OA, in order to prevent disease progression. In patients with CVD or diabetes, intra-articular triamcinolone is preferred over systemic glucocorticoids. Prioritized anti-inflammatory treatments for patients with CKD, gastrointestinal diseases, and OA are recommended. The guideline also introduces emerging therapies, such as interleukin-1 inhibitors and selective urate transport inhibitors, as potential treatment options for refractory cases.

Conclusion: The update offers a comprehensive, patient-centered approach to managing gout, particularly in individuals with associated comorbidities. Multidisciplinary collaboration and emerging new treatments and evidence ensure the optimization of the recommendations.

1 | Introduction

Gout is the most prevalent inflammatory arthritis in adults, especially in men. Biomedical research and clinical studies have focused on gouty arthritis for decades, as have the clinical concerns and guidelines for gout management [1, 2]. Recent evidence underscores that gout is a heterogeneous disease, with about 80% of the gout population having one or more comorbid conditions like metabolic syndrome (MetS), chronic kidney disease (CKD), cardiovascular disease (CVD), hypertension, gastrointestinal disease, and osteoarthritis (OA) [3, 4]. The relationship between gout and those comorbidities remains uncertain, as shared pathogenetic mechanisms, causal effects, and reciprocal interactions have been identified. This evolution of gout complicates management strategies and requires tailored approaches.

The clinical management of gout in patients with comorbidities presents unique challenges, as many of the comorbidities are chronic and require long-term treatment strategies. How to control gout flares in patients with moderate-to-severe CKD, peptic ulcer, and hemorrhage or acute myocardial infarction? Will urate-lowering therapy (ULT) in those patients differ from isolated gouty arthritis? And how to manage gout overlapping OA? These clinical scenarios advocate management strategies and specific medications that may offer mutual benefits to gout and those associated conditions.

The 2019 Chinese Guidelines for the Diagnosis and Treatment of Hyperuricemia and Gout (shorted as 2019 Guidelines) [2], endorsing available evidence by that time, accomplished several weak recommendations addressing ULT in patients with CKD $\geq$ stage 2, and prioritized medications for hypertension, dyslipidemia, and diabetes mellitus. During the past 4 years, emerging novel evidence prompts the possibility for an update of the 2019 Guidelines. This guideline is launched by the Chinese Society of Endocrinology, supported by a multidisciplinary expert group, focusing on both gout and those complicated conditions, aimed to provide optimized options in sophisticated scenarios for clinical practitioners.

2 | Methods

This guideline was developed by the Chinese Society of Endocrinology, following standard procedures and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approaches. A steering committee

of five senior specialists oversaw the process, supported by a multidisciplinary Expert Panel (EP) consisting of 20 endocrinologists, 12 rheumatologists, 7 experts in nephrology, gastroenterology, and cardiology, and 2 methodologists. A Working Group (WG) of 11 junior endocrinologists assisted in guideline development. All participants signed conflict of interest disclosures. The guideline is registered in the International Practice Guidelines Registry Platform under number PREPARE-2024CN563.

In brief, two rounds of surveys were conducted to address key clinical issues, leading to the selection of seven key clinical questions for this guideline. The WG applied the population, intervention, comparison, and outcome (PICO) framework to systematically assess the evidence and prioritize outcomes (Tables S1 and S2). Systematic Literature Reviews (SLRs) were conducted to address each PICO question, focusing on relevant literature published between January 2019 and January 2024. The evidence panel also conducted a rapid review to incorporate the most recent data prior to the guideline publication in March 2025. Major databases such as the Cochrane Library, PubMed, Embase, CNKI, and Wanfang Data were searched for relevant studies, alongside additional searches on resources like Guidelines International Network, National Guideline Clearinghouse, National Institute for Health and Care Excellence, and WHO. The qualities of evidence were assessed and graded using the GRADE system. In total, 2598 records were retrieved, 999 abstracts reviewed, and 103 full-text articles analyzed. The evidence collected was used to prepare evidence bodies for the PICO questions, which were presented to the EP (Table 1). The recommendations were drafted and modified by the EP during the following two meetings and two rounds of Delphi voting. A 10-point visual analog scale (VAS) was used to rate the level of agreement. Consensus was achieved when over 80% of the EP members rated a recommendation with a VAS of ≥ 7 . Figure S1 shows the overall protocol of guideline development. One patient representative was invited to participate in the development process, who fully affirmed the importance of the clinical questions and the shared decision-making model of the recommendation. The final version of recommendations will be distributed through publications, academic meetings, etc.

3 | Results

Seven clinical questions were finalized, and consensus was achieved on 26 recommendations (Table 2 and Figure 1).

TABLE 1 | Seven clinical questions and the literature distribution of each evidence body.

Distribution of evidence (Chapter)					
	Questions	Systematic review/ Meta-analysis	Original research		
		Meta-analysis	Guidelines/Consensus		
1	Gout flare management in patients with chronic kidney disease stage ≥ 3	1 Systematic review 1 Meta-analysis	3 Randomized controlled trials 4 Cohort studies	5 Guidelines 1 Consensus	1 Case report 1 Retrospective study 1 Experimental study
2	Urate-lowering therapy in patients with hyperuricemia/gout combined chronic kidney disease stage ≥ 3	3 Systematic reviews 1 Meta-analysis	3 Randomized controlled trials 4 Cohort studies 4 Cross-sectional studies	0	1 Conference abstract
3	Gout flare management in patients with heart failure or acute myocardial infarction	3 Meta-analyses	7 Randomized controlled trials 6 Cohort studies 1 Case-control study	1 Guideline	1 Case series study
4	Heart failure management in patients with hyperuricemia/gout combined chronic heart failure	1 Systematic review 1 Meta-analysis	12 Randomized controlled trials 1 Cohort study 1 Case-control study 1 Cross-sectional study	0	1 Conference abstract
5	Gout flare management in patients with peptic ulcer or hemorrhage	2 Systematic reviews 2 Meta-analyses	4 Randomized controlled trials 1 Observational study	1 Guideline 1 Consensus	0
6	Glucocorticoid therapy for gout flares in patients with type 2 diabetes	0	1 Cohort study	5 Guidelines 2 Consensus	1 Experimental study
7	Management for patients with both gout and osteoarthritis	1 Systematic review 3 Meta-analyses	2 Randomized controlled trials 2 Cohort studies 1 Cross-sectional study	4 Guidelines 3 Consensus	1 Experimental study

TABLE 2 | Recommendations with grades (GoR), levels of evidence (LoE) and levels of agreement (LoA).

Recommendation	PICO question	GoR	LoE	LoA (%)
Gout flare management in patients with CKD stage ≥ 3				
1. In patients with CKD stage ≥ 3 who are experiencing gout flare, short-term systemic or intra-articular glucocorticoid therapy is recommended	1	2	A	98.4
2. Colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs) should be used with caution	2	2	B	98.4
3. Interleukin-1 (IL-1) inhibitors can be considered as alternative options	2	2	C	98.4
4. In dialysis patients with gout flare, colchicine is contraindicated, NSAIDs or low-dose Anakinra may be considered	3	2	C	98.4
ULT in patients with CKD stage ≥ 3				
5. ULT is recommended in asymptomatic hyperuricemia/gout patients with CKD stage ≥ 3 when SU levels exceed 7 mg/dL (420 μ mol/L), aiming to maintain SU levels below 5 mg/dL (300 μ mol/L)	4,5	2	B	100
6. Febuxostat is recommended as the first-line treatment, and allopurinol as the second-line treatment. Both medications should be initiated at low doses and adjusted based on SU levels and kidney function	6	2	B	100
7. In patients with CKD stage 4–5, febuxostat should not exceed 40 mg/day	7	2	B	100
8. In patients with CKD stage 3–4, allopurinol should be initiated at 50 mg/day, with gradual increases of 50 mg/day every 4 weeks, up to a maximum of 200 mg/day. In patients with CKD stage 5, allopurinol is contraindicated	7	2	C	100
9. Pegloticase can be considered where both drugs are inadequate	6	2	C	100
Gout flare management in patients with heart failure or acute myocardial infarction				
10. In addition to standard therapy for heart failure/myocardial infarction, colchicine may be considered as a preferred treatment for gout flare, administered with regular dosages	8,9	2	C	98.4
11. NSAIDs should be avoided with low-dose aspirin retained	8,9	2	B	98.4
12. In patients who are intolerant or unresponsive to colchicine, short-term glucocorticoids may be considered, as well as IL-1 inhibitors, if available	8,9	2	C	100
Heart failure management in patients with hyperuricemia/gout				
13. In managing heart failure, alongside appropriate ULT, angiotensin receptor-neprilysin inhibitors (ARNI) and sodium-glucose co-transporter 2 (SGLT-2) inhibitors (e.g., dapagliflozin, empagliflozin) are prioritized	10,11	2	B	100
14. Losartan potassium is recommended for initiating hypertension treatment, while switching from other antihypertensives is not advised	10,11	2	C	100
15. Thiazide diuretics should be minimized, and loop diuretics use only with close monitoring and control of SU levels	10,11	2	C	98.4
Gout flare management in patients with peptic ulcer or hemorrhage				
16. In patients at risk of gastrointestinal hemorrhage, selective cyclooxygenase-2 inhibitors are recommended as the preferred treatment over non selective NSAIDs	12	2	B	100
17. In patients with a history of peptic ulcer or hemorrhage, or those with controlled hemorrhage, short-term glucocorticoids are recommended if colchicine is ineffective or intolerant, provided that proton pump inhibitors (PPIs) or mucosal protectants are used concurrently	13	2	B	100

(Continues)

TABLE 2 | (Continued)

Recommendation	PICO question	GoR	LoE	LoA (%)
18. In the case of active hemorrhage, where standard therapy is in the place, short-term parenteral glucocorticoids may be considered, along with Anakinra if deemed appropriate	14	2	C	100
Glucocorticoid therapy for gout flares in patients with type 2 diabetes				
19. In patients with type 2 diabetes experiencing a gout flare, where blood glucose levels are rigorously monitored and controlled, intra-articular triamcinolone acetonide is recommended as the first-line treatment over equivalent systemic glucocorticoid	15	2	C	95.2
Management for patients with comorbid osteoarthritis (OA)				
20. In patients with both gout and OA, appropriate exercise during periods of arthritis relief is recommended	16	2	A	100
21. Additional weight management should be emphasized in those who are overweight or obese	17	1	A	100
22. The initiation of ULT is recommended, irrespective of baseline SU levels, with a target SU range between 180 and 300 $\mu\text{mol/L}$	18	2	B	98.4
23. NSAIDs are preferred analgesic treatment, with a course of 7–10 days	19	1	A	100
24. Long-term use of NSAIDs, exceeding 4 weeks, is not suggested	19	2	B	100
25. Intra-articular glucocorticoid injections are recommended in patients with hip or knee involvements	20	2	C	100
26. Surgical interventions should be considered for refractory pain or disability in large joints when conservative measures fail	21	2	C	98.4

Abbreviation: PICO, population, intervention, comparison, outcome.

3.1 | Recommendations and Explanations

3.1.1 | Gout Flare Management in Patients With CKD Stage ≥ 3

In patients with CKD stage ≥ 3 experiencing gout flare, short-term systemic or intra-articular glucocorticoid therapy is recommended; colchicine and nonsteroidal anti-inflammatory drugs (NSAIDs) should be used with caution; and interleukin-1 (IL-1) inhibitors can be considered as alternative options. In dialysis patients with gout flare, colchicine is contraindicated, while NSAIDs or low-dose Anakinra may be considered.

Western guidelines commonly recommend systemic glucocorticoids as one of the first-line treatments for acute gout, especially in patients with systemic symptoms, or when colchicine or NSAIDs are ineffective or contraindicated, or in those with renal dysfunction, given their comparable pain relief effects during acute gout. Evidence suggests glucocorticoids have minimal impact on kidney function and may even promote renal urate excretion. Despite limited RCT evidence, the EP supports glucocorticoids as the first choice for patients with CKD stage ≥ 3 , without requiring dosage adjustments.

Studies found that colchicine exposure was up to twice as high in patients with moderate or severe renal impairment compared to

those with normal kidney function, with excessive use increasing bone marrow suppression and causing gastrointestinal side effects, which can worsen with higher doses and be fatal. The EP therefore agreed that colchicine use is contraindicated in dialysis patients and should be dosed cautiously in those with renal impairment, with a maximum dose of 0.5 mg/day for moderate impairment (eGFR 30–59 mL/min/1.73 m²). All NSAIDs carry risks in CKD, particularly for renal ischemia, and their use should be avoided long-term in CKD stage ≥ 3 . In dialysis patients, NSAIDs may be considered with close monitoring for adverse effects.

IL-1 inhibitors, such as Anakinra (IL-1 receptor antagonist), Canakinumab (anti-IL-1 β monoclonal antibody), and Rilonacept (soluble IL-1 decoy receptor), are recommended when other therapies are insufficient [1]. Anakinra has shown non-inferior to conventional treatments, with safety profiles comparable to those of glucocorticoids. A multicenter retrospective study has reported that Anakinra may be a safe option for gout patients with CKD stage 4–5 [5]. Further evidence is needed to confirm the efficacy and safety of the other two drugs in patients with CKD stage ≥ 3 [6]. Therefore, IL-1 inhibitors require careful consideration in patients with severe renal impairment (eGFR < 30 mL/min/1.73 m²) or those on dialysis, with reduced dosing (e.g., Anakinra 100 mg every other day) recommended. Long-term use requires monitoring for neutropenia, and IL-1 antagonists are contraindicated in patients with active infections.

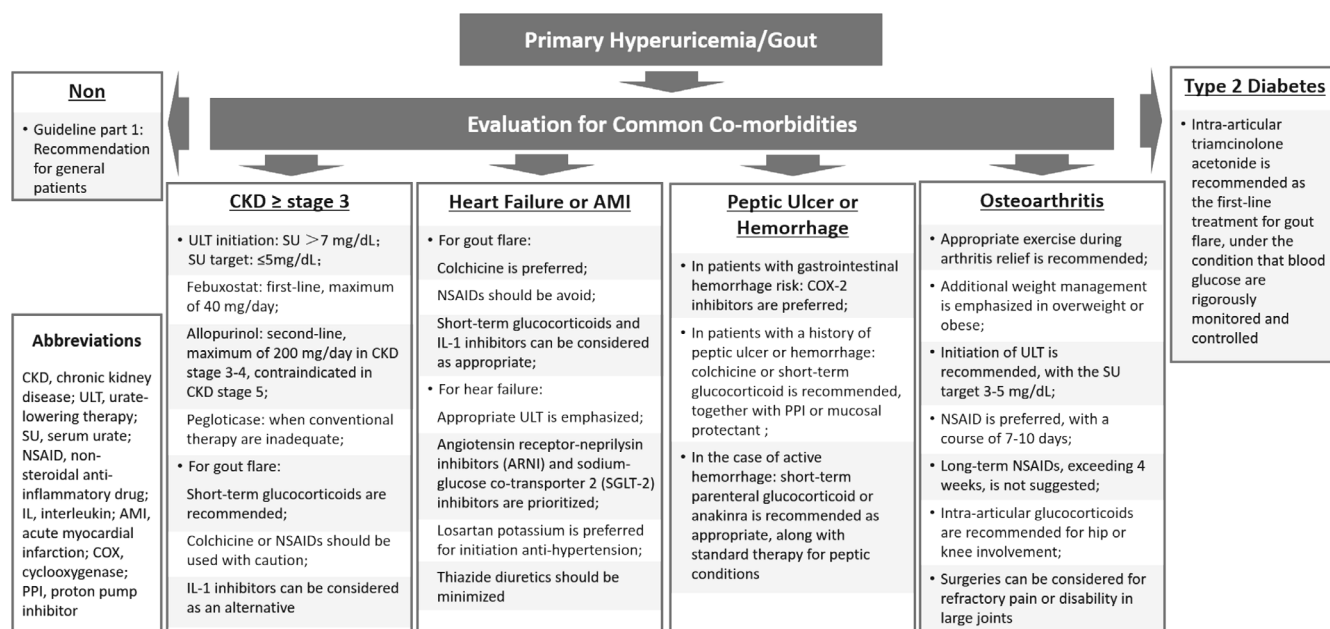


FIGURE 1 | Flow chart of recommendations.

3.1.2 | ULT in Patients With CKD Stage ≥ 3

ULT is recommended in patients with CKD stage ≥ 3 when SU levels exceed 7 mg/dL (420 μ mol/L), aiming to maintain SU levels below 5 mg/dL (300 μ mol/L). Febuxostat is recommended as the first-line treatment, and allopurinol as the second-line treatment. Both medications should be initiated at low doses and adjusted based on SU levels and kidney function. Febuxostat should not exceed 40 mg/day in patients with CKD stage 4–5. Allopurinol should be initiated at 50 mg/day, with gradual increases of 50 mg/day every 4 weeks, up to a maximum of 200 mg/day in patients with CKD stage 3–4, and is contraindicated in patients with CKD stage 5. Pegloticase can be considered where both drugs are inadequate.

Hyperuricemia is an independent risk factor for the development and progression of CKD. Systemic reviews and RCTs show that ULT, particularly with febuxostat, can slow CKD progression in patients with asymptomatic hyperuricemia and CKD stage 3–4 [7]. Studies have shown that the prevalence of CKD stage ≥ 3 increases with the higher SU levels, and maintaining SU levels below 300 μ mol/L has an 11% lower risk of CKD deterioration [8]. Based on current evidence, the EP recommended maintaining sUA levels below 300 μ mol/L in patients with hyperuricemia and CKD stage 3, to prevent further kidney deterioration.

Febuxostat, eliminated via renal and biliary pathways, requires no dose adjustment for mild to moderate renal impairment, making it the preferred xanthine oxidase inhibitor in CKD patients. Allopurinol is associated with an increased risk of severe skin reactions in renal failure. Topiroxostat, primarily metabolized by the liver, offers potential benefits for patients with renal insufficiency. Both febuxostat and topiroxostat effectively prevent eGFR decline in CKD patients with hyperuricemia, outperforming other urate-lowering drugs [9, 10]. For eGFR < 30 mL/min/1.73 m², febuxostat's safety and efficacy at 20–40 mg/

day are well-established [11]. Uricosurics like benzbromarone should be avoided in patients with CKD stage > 3 or urolithiasis. Pegloticase has proved its efficacy and safety in patients with CKD stage 3–5 who were refractory to conventional ULT [12, 13]. A study in gout patients receiving hemodialysis showed no significant effect of hemodialysis on pegloticase administration, indicating its feasibility in these patients [14]. Although it does not have market access in China, this updated guideline provides an option for gout patients with severe renal diseases based on the clinical evidence presented here.

3.1.3 | Gout Flare Management in Patients With Heart Failure or Acute Myocardial Infarction

In addition to standard therapy for heart failure/myocardial infarction, colchicine may be considered as a preferred treatment for gout flare, administered with regular dosages; NSAIDs should be avoided with low-dose aspirin retained. In patients who are intolerant or unresponsive to colchicine, short-term glucocorticoids may be considered, as well as IL-1 inhibitors, if available.

Several studies indicated that NSAIDs increase the risk of adverse cardiovascular events, such as acute myocardial infarction and heart failure. Guidelines recommended avoiding NSAIDs in heart failure due to their potential to cause water and sodium retention, increase systemic vascular resistance, and reduce diuretic efficacy, all of which may worsen heart failure [15]. Based on this evidence, the EP agreed that NSAIDs should be avoided for gout flare in patients with heart failure or acute myocardial infarction.

Colchicine has demonstrated potential cardiovascular protective effects, reducing inflammation and stabilizing plaques, which may prevent myocardial infarction [16, 17]. A cohort study showed that colchicine reduced cardiovascular events in

gout patients, making it safe and effective for pain relief during gout flares in patients with heart failure or myocardial infarction, while potentially reducing cardiovascular risks.

The safety of glucocorticoids for gout flares in these patients is less clear. Short-term (<4 weeks) glucocorticoid therapy has shown benefit in patients with heart failure, but long-term use may increase cardiovascular risk, mainly due to fluid retention.

Anakinra using in short term has shown efficacy in gout patients with heart failure who were intolerant or resistant to colchicine, without raising infection risk [18], though its high cost and long-term infection risk limit its use. Canakinumab [19, 20] and rilonacept [21] may reduce cardiovascular events but have not been studied for gout flares in heart failure or myocardial infarction patients.

3.1.4 | Heart Failure Management in Patients With Hyperuricemia/Gout

In managing heart failure, alongside appropriate ULT, angiotensin receptor-neprilysin inhibitors (ARNI) and sodium-glucose co-transporter 2 (SGLT-2) inhibitors (e.g., dapagliflozin, empagliflozin) are prioritized; losartan potassium is recommended for initiating hypertension treatment, while switching from other antihypertensives is not advised; thiazide diuretics should be minimized, and loop diuretics used only with close monitoring and control of SU levels.

In patients with asymptomatic hyperuricemia or gout combined with heart failure, strict control of SU levels has been recommended. Febuxostat has been suggested to be used with caution in patients with CVD. In recent years, ARNI [22] and SGLT2 inhibitors [23–25] have become key therapies for heart failure. Small studies suggest that ARNI can lower SU levels in heart failure patients, regardless of baseline levels [26]. A randomized controlled study [27] showed that ARNI reduced cardiovascular mortality and heart failure-related hospitalizations, alongside lowering SU levels, compared to valsartan in patients with heart failure and hyperuricemia.

SGLT2 inhibitors, initially developed for diabetes, reduce renal glucose reabsorption and promote urinary excretion. These drugs have been shown to lower the risks of heart failure hospitalization and cardiovascular mortality in both diabetic and nondiabetic patients. Studies confirmed their urate-lowering effect, with dapagliflozin reducing SU by 0.84 mg/dL (50 μ mol/L) in heart failure patients [28]. The EMPEROR-Reduced trial [29] showed that empagliflozin reduced SU by 1.12 mg/dL (67 μ mol/L) and decreased gout flare frequency. A multicenter trial found that a high dose of losartan potassium (150 mg/day) reduced SU levels by 0.27 mg/dL (16 μ mol/L) and hyperuricemia incidence in patients with heart failure.

Diuretics, commonly used in heart failure, can elevate SU levels and trigger gout, possibly through reduced blood volume, increased renal urate reabsorption, and potassium-depleting effects. Potassium-sparing diuretics, like spironolactone, should be used cautiously. The TOPCAT study showed that spironolactone

had no significant effect on SU but improved heart failure outcomes [30], and a case-control study found it reduced gout flares in heart failure patients.

3.1.5 | Gout Flare Management in Patients With Peptic Ulcer or Hemorrhage

In patients at risk of gastrointestinal hemorrhage, selective cyclooxygenase (COX)-2 inhibitors are recommended as the preferred treatment over nonselective NSAIDs. In patients with a history of peptic ulcer or hemorrhage, or those with controlled hemorrhage, short-term glucocorticoids are recommended if colchicine is ineffective or intolerant, provided that proton pump inhibitors (PPIs) or mucosal protectants are used concurrently. In the case of active hemorrhage, where standard therapy is in place, short-term parenteral glucocorticoids may be considered, along with Anakinra, if deemed appropriate.

NSAIDs remain the first-line treatment for gout flares. In elderly patients and those with a history of peptic ulcer, hemorrhage, or perforation, drugs with rapid action and fewer gastrointestinal side effects are preferred. Selective COX-2 inhibitors, such as etoricoxib and celecoxib, have demonstrated similar efficacy in pain relief with fewer gastrointestinal side effects compared to nonselective NSAIDs like indomethacin and diclofenac.

In patients with a history of peptic ulcer or hemorrhage, colchicine may be considered, with short-term glucocorticoids serving as alternatives when colchicine is ineffective or poorly tolerated. Glucocorticoids offer comparable pain relief to NSAIDs but with fewer gastrointestinal adverse events, including indigestion, nausea, vomiting, and gastrointestinal hemorrhage [31]. A RCT indicated that for patients with peptic ulcer hemorrhage and gout flare, short-term use of methylprednisolone (with PPI) was more effective and safer than celecoxib [32]. Furthermore, a single intramuscular injection of mixed betamethasone (7 mg) demonstrated better outcomes and fewer adverse reactions than a diclofenac sodium regimen.

Anakinra has proven effective and safe for treating gouty arthritis, especially in patients with severe or complicated conditions where traditional treatments are inadequate [33]. Anakinra (100 mg/day, subcutaneous injection for 5 days) is comparable in efficacy to conventional treatments, with fewer gastrointestinal side effects. The pain relief effects are similar between the Anakinra 100 mg/day and the 200 mg/day groups during the study period of 5 days. However, agents like Canakinumab and Rilonacept are not recommended for gout patients with gastrointestinal hemorrhage due to insufficient evidence supporting their safety in this context.

3.1.6 | Glucocorticoid Therapy for Gout Flares in Patients With Type 2 Diabetes

In patients with type 2 diabetes experiencing a gout flare, where blood glucose levels are rigorously monitored and controlled, intra-articular triamcinolone acetonide is recommended as the first-line treatment over equivalent systemic glucocorticoid.

This approach is preferred over equivalent systemic glucocorticoids, such as oral prednisone, intramuscular mixed betamethasone, or intravenous dexamethasone sodium phosphate.

Cohort studies indicated consistently that systemic glucocorticoids were related to an increased risk of diabetes mellitus [34]. Blood glucose levels might rise at 24–72 h after the administration of glucocorticoid [35], leading to a recommendation for limited use of glucocorticoids in diabetic patients. Synovial fluid aspiration and intra-articular glucocorticoid injection are prioritized for acute gouty arthritis, especially in large joints. Triamcinolone acetonide has low solubility in synovial fluid, providing prolonged anti-inflammatory effects, making it superior to systemic glucocorticoids when administered with an appropriate dose [2]. However, joint infection must be ruled out, and repeated injections should be avoided.

If systemic glucocorticoids are necessary, oral prednisone or equivalent is preferred at 0.5 mg/kg/day, with discontinuation after 3–5 days for the sake of blood glucose control. Betamethasone and dexamethasone both have high anti-inflammatory potency, making them better substitutes for short-term systemic glucocorticoids.

3.1.7 | Management for Patients With Comorbid OA

In patients with both gout and OA, appropriate exercise during periods of arthritis relief is recommended; additional weight management should be emphasized in those who are overweight or obese; the initiation of ULT is recommended, irrespective of baseline SU levels, with a target SU range between 180 and 300 $\mu\text{mol/L}$; NSAIDs are the preferred analgesic treatment, with a course of 7–10 days; long-term use of NSAIDs, exceeding 4 weeks, is not suggested; intra-articular glucocorticoid injections are recommended in patients with hip or knee involvement; surgical interventions should be considered for refractory pain or disability in large joints when conservative measures fail.

A meta-analysis underscores the significant benefits of therapeutic exercise in improving pain and physical function in patients with OA [36]. The 2023 NICE guideline for OA management recommends informing overweight or obese patients that weight loss can enhance physical function, reduce pain, and improve quality of life [37]. Regular, moderate physical activity has been shown to reduce CRP levels, decrease gout flares, and alleviate pain. Overweight and obesity are strongly associated with elevated SU levels and increased risk of gout flares, and weight loss can lower SU levels by 30–168 $\mu\text{mol/L}$, reducing recurrent flares [38]. In obese men, weight loss not only reduced SU levels but also prevented the development of gout. The OPPORTUNITY study demonstrated that adherence to nonsurgical interventions including exercise and weight loss significantly improved the quality of life in OA patients [39]. Therefore, the EP recommends moderate exercise and weight management for patients with both gout and OA.

A retrospective study found that SU level correlated with synovitis and soft tissue swelling in knee OA patients, as measured by MRI [40]. As a result, this guideline suggests a more aggressive

ULT strategy, aiming for a target SU range of 180–300 $\mu\text{mol/L}$ to prevent disease progression.

A systematic review and meta-analysis found no benefit of colchicine in reducing pain in OA patients [41]. In contrast, a study showed that etoricoxib significantly improved pain relief, joint function, and quality of life in elderly OA patients [42]. However, due to the risk of gastrointestinal, cardiovascular, and other adverse events, long-term NSAID use is not recommended [43]. Chronic NSAID use has also been linked to increased joint pain, stiffness, and disability, accelerating the need for knee replacement in OA patients [44]. Therefore, NSAID use should be limited to no more than 4 weeks; alternative treatments should be considered beyond this duration.

Intra-articular glucocorticoid injections are effective for managing hip or knee OA, especially in patients with moderate-to-severe pain and joint effusion. The Multidisciplinary Italian Consensus advises their use for short-term pain relief, with caution regarding repeated injections. A RCT showed that intra-articular triamcinolone acetonide (40 mg, every 3 months for 2 years) increased cartilage loss compared to saline injections [45]. Repeated glucocorticoid injections should generally not exceed four per year [46].

When nonsurgical treatments fail and quality of life is severely impacted, the NICE Clinical Practice Guideline for OA suggests considering joint replacement surgery [37]. The Malaysian consensus recommends knee replacement surgery for advanced knee OA patients, with joint replacement considered for those with persistent pain and functional decline.

4 | Discussion

Gout has evolved from a rare inflammatory arthritis to a common disorder worldwide, frequently accompanying a range of diseases that are typically associated with a severe socioeconomic burden [47]. Some comorbidities are considered with shared mechanisms, like hypertension, CVD, stroke, obesity, hyperlipidemia, type 2 diabetes mellitus, and CKD, which are now clustered as cardiometabolic-renal (CMR) conditions. Studies on gout populations from Britain, France, China, and the US showed consistently a high prevalence of those conditions [3, 48]. OA is another common arthritis, which has long been linked to gout due to the epidemiological consistency. The prevalence of knee OA in a gout cohort was reported as high as 68%, and the disease outcomes tend to be more severe in such patients [4]. Besides, some complications, like peptic ulcer disease, hyperglycemia, hypertension, and cardiac dysfunction, are unavoidable in a population with repeated or long-term NSAIDs and glucocorticoids [49]. These comorbidities and complications have made gout management a clinical challenge in these patients who are usually grouped as difficult to treat [50]. In the past decade, novel drugs in the related fields have become commercially available, producing new comprehensive management approaches that may serve as evidence addressing those problems.

The auto-inflammatory nature of gout has gradually been recognized. However, MSU crystal deposition and phagocytosis are

always the first signals of a gout flare. Long-term ULT to maintain SU at target levels to avoid MSU crystal formation or promote its resolution is the core of gout management, as indicated by previous guidelines [1, 2]. In addition to symptomatic gout, asymptomatic hyperuricemia has been associated with injuries to the kidneys, vascular intima, as well as joints, visualized by advanced imaging measures in recent years, like dual-energy CT [4]. According to the 2019 FREED study, lowering SU to below 5 mg/dL with febuxostat delayed the progression of kidney dysfunction in patients with hyperuricemia at risk for cerebral, cardiovascular, or renal disease (Supplementary Reference 86). Based on these updates, the stricter SU goal of < 5 mg/dL in hyperuricemia/gout patients with CKD stage ≥ 3 was ultimately agreed by the EP. Furthermore, this guideline recommends febuxostat as the preferred choice, due to the higher risk of hypersensitivity to allopurinol in Asian populations, particularly in cases of impaired renal function.

Heart failure can be the consequence of both the CMR condition and side effects from NSAIDs and glucocorticoids. Diuretics are the key medication for heart failure, which are also the most common drugs associated with hyperuricemia and gout. Fortunately, two novel categories of anti-heart failure medications, the angiotensin receptor-neprilysin inhibitors (ARNI) and the sodium-glucose cotransporter-2 (SGLT-2) inhibitors, have been proved to be effective not only for heart failure but also for lowering SU levels [27–29]. SGLT-2 inhibitors (dapagliflozin or empagliflozin), in particular, improve several components of metabolic syndrome, while also slowing CKD progression and reducing the risk of major cardiovascular events and premature death. Therefore, SGLT-2 inhibitors may offer multiple benefits in treatment of heart failure patients with comorbid hyperuricemia.

Gout flare management tends to be sophisticated when patients are complicated with conditions like CKD, acute myocardial infarction, heart failure, diabetes, and peptic ulcer or hemorrhage. On the other hand, recurrent gouty arthritis may have adverse impacts on the prognosis of CVDs. In these patients, treatments with colchicine, NSAIDs, or glucocorticoids are restricted to some conditions that are hard to systemically acquire. This guideline accomplishes detailed recommendations addressing these clinical dilemmas, combining evidence from relevant fields and new drugs. For example, colchicine is prioritized for the prophylaxis or termination of gout flare in patients with heart failure or acute myocardial infarction due to the benefits of both gout and heart disease from low-dose colchicine confirmed by multiple studies [16, 17]. Biotherapy is the main progression in clinical therapy in recent years, with piled evidence in gout management. The efficacy and safety of IL-1 inhibitors for gout flares in patients inappropriate for traditional anti-inflammatory medicine have been verified by several RCTs [5, 18, 20, 21]. One novel IL-1 β inhibitor, firscekibart, is now commercially available in China, which encourages the recommendations of IL-1 inhibitors in this guideline.

Although patients with gout are frequently complicated with OA, gout overlapping OA is seldom considered in previous management guidelines. OA is primarily a condition of chondrocyte degeneration, resulting from the “wear-and-tear” mechanism. The alteration of synovial lining permeability and synovial

fluid physiochemical environment, and the cartilage fibrillation in OA may facilitate urate supersaturation, promote urate crystallization and deposition, while the latter in turn activates synovial lining macrophages and results in the generation of inflammatory mediators, particularly IL-1 β , which may contribute to further OA cartilage degradation [47]. These clinical and experimental studies suggest that gout and OA exacerbate reciprocally when coexisting in the same joints. Giving full consideration to these studies and integrating the monotherapy approaches for both conditions, this guideline provides comprehensive recommendations for managing gout combined with OA, including lifestyle interventions, stricter SU control, appropriate anti-inflammatory therapy, and surgical intervention.

In summary, this updated guideline provides comprehensive management recommendations for gout with comorbidities, guaranteed by multidisciplinary collaboration. This guideline echoed the 2018 EULAR recommendations for evaluation of comorbidities once gout is diagnosed, while focused on factors related to the Chinese population and traits of gout in China. Novel drugs (dotinurad, topirostat, tigulixostat, AR882, rizinurad/SHR4640, etc.) are emerging, promising the next update in the future (Supplementary Reference 96).

Author Contributions

Changgui Li conceived the idea and submitted the project to the Chinese Association of Endocrinology Executive Committee. Jiajun Zhao co-chaired the meetings. Changgui Li was in charge of the whole process of the guideline development. Mingshu Sun wrote the manuscript with the help from Zhen Liu, Yuwei He, Xinde Li, Fei Yan, Lin Han, Xufei Luo, and Can Wang conducted most of the data collection, literature searching, and evidence retrieving. Ronald ML Yip provided opinions as an external reviewer. All authors have contributed to this work and have approved the final version of the manuscript.

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Ethics Statement

This study does not involve human participants.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Additional references are presented in Supplementary Reference.

Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Figure S1:** Flow chart of guideline development. **Table S1:** Clinical questions and PICO deconstruction. **Table S2:** Importance of outcome indicator.