GOUT

CHI Formulary Indication Review

مجلس الضمان الصحي
Council of Health Insurance

INDICATION UPDATE

ADDENDUM- October 2023

To the CHI Original Gout Clinical Guidance- Issued February 2020

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- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

ACP	American College of Physicians
ACTH	Adrenocorticotropic Hormone
AHU	Asymptomatic Hyperuricemia
CADTH	Canadian Agency for Drugs and Technologies in Health
CHI	Council of Health Insurance
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
DM	Diabetes Mellitus
EMA	European Medicines Agency
FDA	Food and Drug Administration
HAS	Haute Autorite de Sante
HLA-B5801	Human Leukocyte Antigen–B5801
HTA	Health technology assessment
IL-1	Interleukin-1
IQWIG	Institute for Quality and Efficiency in Health Care
NICE	National Institute for Health and Care Excellence
NPO	Nothing by Mouth
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PBAC	Pharmaceutical Benefits Advisory Committee
PMDA	Pharmaceuticals and Medical Devices Agency
SC	Subcutaneous
SFDA	Saudi Food and Drug Authority
SU	Serum Uric Acid
sUA	Serum Urate
ULT	Urate-Lowering Therapy
XOI	Xanthine Oxidase Inhibitors

Executive Summary

Gout is a type of inflammatory arthritis characterized by recurrent episodes of synovitis, which cause joint swelling and pain. These episodes are known as acute gouty arthritis flares or attacks. The condition can progress to a chronic state, leading to the development of tophi. Tophi are solid deposits of monosodium urate (MSU) crystals that form in various parts of the joints, cartilage, tendons, bursae, bone, and soft tissue, resulting in a condition called chronic tophaceous gout. The distinction between acute intermittent and chronic intermittent conditions is not clear-cut. However, the advanced stage of gout is marked by more persistent joint manifestations and the presence of tophi, which may either be clinically apparent or concealed within the joint[1].

Gout flares manifest abruptly and may persist for days or even weeks. After these flares, extended periods of remission follow, lasting for weeks, months, or even years, during which no symptoms are experienced before another flare-up occurs. Typically, gout affects only one joint at a time, frequently targeting the big toe. Additionally, the lesser toe joints, ankle, and knee are commonly affected as well. Symptoms in the affected joint(s) typically include intense pain, swelling, redness, and heat[2].

Gout can be diagnosed by confirming the existence of uric acid crystals in synovial fluid or within a tophus. When dealing with a sudden gout episode, extracting joint fluid through a needle, and analyzing it using polarized light can provide a conclusive diagnosis. The distinct diagnostic feature in this case is the identification of uric acid crystals with needle-like shapes that display negative birefringence (appearing yellow when aligned with the polarization axis). Additionally, the presence of intracellular crystals within neutrophils is a typical observation during an acute gout attack[3].

Gout, the most prevalent type of inflammatory arthritis, has been on the rise. The latest estimate of its prevalence among adults in the United States, as derived from the 2007-08 National Health and Nutrition Examination Survey (NHANES) data, stands at 3.9 percent, which translates to approximately 8.3 million individuals affected. The prevalence differs between genders, with a rate of 2.0 percent in women and 5.9 percent in men, representing an increase compared to previous NHANES data cycles[1].

The increase in the prevalence of gout has closely followed the rise in the occurrence of coexisting conditions linked to hyperuricemia, which is the primary risk factor for gout. These associated conditions include obesity, hypertension, hypertriglyceridemia, hypercholesterolemia, type 2 diabetes, metabolic syndrome, chronic kidney disease, and renal insufficiency. Moreover, the augmented use of medications that elevate the risk of developing hyperuricemia, such as thiazide

diuretics, low-dose aspirin, or their combination, may also contribute to the growing prevalence of gout[1].

Globally, there has been a rise in the incidence of gout. In recent years, the lifestyle of Arab individuals has undergone a shift towards a more Westernized pattern, characterized by increased consumption of meat, as incomes and resources have grown. This shift has contributed to higher occurrences of hyperuricemia, gout, obesity, hypertriglyceridemia, and diabetes, particularly in developing countries[4].

The purpose of the recent publications in Saudi Arabia was to assess gout disease knowledge among male and female adults in certain locations (Riyadh, Saudi Arabia, 2020) and in Taif city (2020).

A study published in Rheumatology International in 2001 examined the prevalence of hyperuricemia in Saudi Arabia. The study involved 487 individuals, and the findings revealed that only 8.42% of the participants had hyperuricemia[5].

When deciding on the suitable treatment for patients with gout, it is essential to carefully consider any comorbidities and contraindications they may have. Gout treatment aims to achieve two main objectives: firstly, to relieve the pain and inflammation caused by acute gout attacks, and secondly, to manage the condition in the long term by reducing serum urate (sUA) levels, thereby minimizing the risk of future attacks. The management of acute attacks can be challenging, particularly due to the presence of other chronic health conditions that often coexist with gout, such as diabetes mellitus (DM), chronic kidney disease (CKD), hypertension, and cardiovascular disease (CVD). Taking these patient characteristics into account is crucial for effective gout treatment[6].

CHI issued Gout clinical guidance after thorough review of renowned international and national clinical guidelines in February 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Gout clinical guidance and seeks to offer guidance for the effective management of Gout. It provides an update on the Gout Guidelines for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing the most updated best available clinical and economic evidence related to drug therapies.

Main triggers for the update are summarized, being the addition of new guidelines namely; American College of Rheumatology Guideline for the Management of Gout, 2020, The Italian Society of Rheumatology clinical practice guidelines for the diagnosis and management of gout, 2019, Asia-Pacific League of Associations for Rheumatology clinical practice guideline for treatment of gout, 2021 Japanese Society of Gout and Uric & Nucleic Acids Guidelines for Management of Hyperuricemia and Gout 3rd edition, 2019, NICE guidelines 2022; Gout: diagnosis and

management, The Hong Kong Society of Rheumatology consensus recommendations for the management of gout 2023.

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to include the SFDA registered drug Anakinra in the CHI formulary while removing Acemetacin as it is no longer registered on the SFDA Drug List of June 2023. A new drug molecule that is FDA approved, non-SFDA registered can also be considered for refractory gout; Pegloticase. Probenecid, an uricosuric Agent that is non-SFDA registered, can also be considered for the treatment of hyperuricemia associated with gout or gouty arthritis. Finally, canakinumab gained FDA approval in August 2023 for the treatment of gout flares in adults who cannot be treated with NSAIDs, colchicine, or repeated courses of corticosteroids, and in people who could not tolerate or had an inadequate response to NSAIDs or colchicine[7].

There have been changes or updates made to the previously listed drugs in terms of drug information and prescribing edits since February 2020; Acemetacin is no more SFDA approved. Zurampic (Lesinurad) and Duzallo (Allopurinol / Lesinurad) are withdrawn from the market. *FDA announced the discontinuation of* ***Zurampic*** *(lesinurad) as of February 1, 2019. The discontinuation was due to business reasons, and not due to any safety, efficacy, or quality issues*. Prescribing edits were added to Canakinumab, Colchicine and Febuxostat. Modifications were done to the maximum dose of Allopurinol and Colchicine.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in the Gout therapeutic management.

Below is a table summarizing the major changes based on the different gout guidelines used to issue this report:

Table 1. General Recommendations for the Management of Gout

Management of Gout		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
Strongly recommend **allopurinol** over all other ULTs as the preferred first-line agent for all patients, including those with CKD stage >3.	Moderate	ACR, 2020
Strongly recommend starting **allopurinol** and **febuxostat** at a low dose with subsequent dose titration to target.	Moderate	ACR, 2020

For patients with gout taking **febuxostat** with a history of CVD or a new CV event, it is conditionally recommended switching to an alternative ULT agent if available and consistent with other recommendations in this guideline.	Moderate	ACR, 2020
Strongly recommend initiating **concomitant anti-inflammatory prophylaxis therapy** (e.g., colchicine, nonsteroidal anti-inflammatory drugs [NSAIDs], prednisone/ prednisolone) over no anti-inflammatory prophylaxis. The choice of specific prophylaxis should consider patient factors.	Moderate	ACR, 2020
For all patients taking ULT, it is strongly recommended to continue ULT to achieve and maintain an **SU target of <6 mg/dl** over no target.	High	ACR, 2020
For patients with gout where XOI, uricosurics, and other interventions have failed to achieve SU target and who have frequent gout flares or non-resolving subcutaneous tophi, it is strongly recommended switching to **pegloticase** over continuing current ULT	Moderate	ACR, 2020
For patients experiencing a gout flare, it is strongly recommended using oral **colchicine**, **NSAIDs**, or **glucocorticoids** (oral, intraarticular, or intramuscular) as appropriate first-line therapy for gout flares over IL-1 inhibitors or ACTH (the choice of colchicine, NSAIDs, or glucocorticoids should be made based on patient factors and preferences).	High	ACR, 2020
When colchicine is the chosen agent, it is strongly recommended to give low-dose colchicine over high-dose colchicine, given its similar efficacy and fewer adverse effects.	High	ACR, 2020

A low-dose regimen of colchicine (1.5-1.8 mg/d) is preferred over a high-dose regimen (4.5-4.8 mg/d) to reduce pain	Strong recommendation, high quality of evidence	Asia-Pacific League of Associations for Rheumatology, 2021
For patients who may receive NPO (Nothing per mouth), it is strongly recommend glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH (Adrenocorticotropic Hormone).	High	ACR, 2020
For acute gout attacks, it's crucial to initiate treatment promptly, preferably within 12 hours. Patients should be educated to self-administer medication at the initial onset of symptoms.	Level of Evidence: 1B	Hong Kong Society of Rheumatology, 2023
First-line therapy in **acute gout flares** ➢ Recommended initial options for treating acute gout flares are colchicine and/or an NSAID or COXIB. Oral corticosteroids, articular aspiration, and corticosteroid injections are also appropriate options (1, A oral; 3, C intra-articular, intramuscular). The choice of medication should be discussed with the patient and based on the presence of co-morbidities, contraindications, and the number and type of affected joints (5, D). Initial combination therapy is an appropriate option for a severe gouty attack (5, D).	Level 1-5; Strength A-D	Italian Society of Rheumatology, 2019
Second line and adjunctive therapies in **acute gout flares** ➢ If the response to the first-line therapy is insufficient, switching to alternative therapy or using combination therapy is indicated (5, D). In non-responders and patients with contraindications to colchicine, NSAIDs, COXIBs, and	Level 1-5; Strength A-D	Italian Society of Rheumatology, 2019

corticosteroids (oral and injectable), IL-1 inhibitors may be considered. (1, A canakinumab; 4, D anakinra).		
First-line ULT in **gout** ➢ For patients with normal kidney function, allopurinol is the recommended first-line ULT (2, B). The starting dosage of allopurinol should be low (no greater than 100 mg/ day for any patient) and increased if necessary to reach the target SUA level (1, A).	Level 1-2; Strength A-B	Italian Society of Rheumatology, 2019
Second line and combination ULTs in gout ➢ If the SUA target cannot be achieved with an appropriate dose of **allopurinol** or if allopurinol is not tolerated, alternatives such as **febuxostat** can be considered (1, A). ➢ **Uricosuric agents** may be used in patients resistant to or intolerant of xanthine oxidase inhibitors (1, A). ➢ **Combination therapy with a uricosuric agent and xanthine oxidase inhibitor** can be used in patients not achieving the therapeutic SUA target with monotherapy (3, C). ➢ **Uricase** as monotherapy should be reserved for severe gout cases where other therapies have failed or are contraindicated (2, C)	Level 1-3; Strength A-C	Italian Society of Rheumatology, 2019
For patients with gout who've encountered their first attack and possess markedly elevated serum urate levels (>0.54 mmol/L [9 mg/dL]) or have an early onset of the condition (age<40 years), the option of ULT might be considered.	Level of Evidence: 1B	Hong Kong Society of Rheumatology, 2023

Flare prophylaxis ➢ Prophylaxis should be initiated with, or just prior to initiating, ULT and the recommended prophylactic treatment is **colchicine** (1, A). ➢ In patients who cannot tolerate colchicine or if colchicine is contraindicated, a **low-dose NSAID or COXIB** can be used as an alternative providing there are no contraindications or intolerance to NSAIDs or COXIBs (1, A). ➢ If colchicine, NSAIDs and COXIBs are contraindicated, not tolerated, or ineffective, **low dose glucocorticoids** may be used (5, D). (Level 1-5; Strength A-D)	Level 1-5; Strength A-D	Italian Society of Rheumatology, 2019
Consider adding a proton pump inhibitor for people with gout who are taking an NSAID or a corticosteroid to prevent gout flares when starting or titrating ULT. Take into account the person's individual risk factors for adverse events	Not graded	NICE, 2022
Tophi ➢ Tophi should be treated medically by achieving a sustained reduction in SUA (2, B). ➢ Surgery is only indicated in selected cases (e.g., nerve compression, mechanical impingement, or infection) (2, B).	Level 1-2; Strength A-B	Italian Society of Rheumatology, 2019
Treatment of chronic tophaceous gout ➢ The use of a XOI (**allopurinol** or **febuxostat**) is recommended over no ULT to achieve resolution of tophi in patients with chronic tophaceous gout.	Strong recommendation, low quality of evidence	Asia-Pacific League of Associations for Rheumatology, 2021
➢ Adding **lesinurad** to a **XOI** for resolution of tophi in chronic	Weak recommendation,	Asia-Pacific League of

tophaceous gout patients with serum uric acid levels >6 mg/dL is not recommended	moderate quality of evidence	Associations for Rheumatology, 2021
Colchicine ➢ Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors, such as cyclosporin or clarithromycin, should be avoided (1, A). ➢ In cases of renal impairment or statin treatment, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine (2, B). ➢ If loop or thiazide diuretics are being used to treat hypertension rather than heart failure, substitution of the diuretic is recommended, if possible and an alternative antihypertensive agent can be considered (4, D).	Level 1-4; Strength A-D	Italian Society of Rheumatology, 2019

Table 2. New Drug Molecules and HTA Analysis

New Molecules			
	Drug	**Drug Class**	**HTA Recommendations**
SFDA Registered	Anakinra	Interleukin-1 Receptor Antagonist	No HTA recommendations
Non-SFDA Registered	Pegloticase	Urate-Oxidase (Recombinant) Enzyme	

At the end of the report, a key recommendation synthesis section is added highlighting the latest updates in Gout clinical and therapeutic management, and appendices are available for further information.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: one part includes recommendations from updated versions of guidelines mentioned in the previous CHI Gout report, and another part includes newly added guidelines that have helped generate this report.

1.1 Revised Guidelines

There are no updated versions of the guidelines detailed in the February 2020 CHI Gout Report.

Table 3. Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated versions**
Section 1.1 Management of Acute and Recurrent Gout: A Clinical Practice Guideline from the American College of Physicians 2017	N/A*
Section 1.2 2016 updated EULAR (European League Against Rheumatism) evidence-based recommendations for the management of gout	N/A*
Section 1.3 The British Society for Rheumatology Guideline for the Management of Gout 2017	N/A*

*: *No updated versions available*

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI Gout report, along with their recommendations.

Table 4. List of Additional Guidelines

Additional Guidelines
Section 1.2.1. 2020 American College of Rheumatology Guideline for the Management of Gout[8]

Section 1.2.2. The Italian Society of Rheumatology clinical practice guidelines for the diagnosis and management of gout 2019[9]
Section 1.2.3. 2021 Asia-Pacific League of Associations for Rheumatology clinical practice guideline for treatment of gout[10]
Section 1.2.4. Japanese Society of Gout and Uric & Nucleic Acids 2019 Guidelines for Management of Hyperuricemia and Gout 3rd edition[11]
Section 1.2.5. NICE guidelines; Gout: diagnosis and management[12]
Section 1.2.6. The Hong Kong Society of Rheumatology Consensus Recommendations for the Management of Gout (2023)[13]

1.2.1 2020 American College of Rheumatology Guideline for the Management of Gout

The American College of Rheumatology Guideline's Level of evidence and recommendation grades are outlined below[8]:

Table 5. GRADE Certainty Ratings

Certainty	Definition
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
High	The authors have a lot of confidence that the true effect is similar to the estimated effect

The American College of Rheumatology's recommendations are assigned the class of recommendations defined in the preceding table:

1. Indications for pharmacologic urate-lowering therapy (ULT):
    - Strongly recommend initiating ULT for patients with 1 or more subcutaneous tophi over no ULT. (High)
    - Strongly recommend initiating ULT for patients with radiographic damage attributable to gout over no ULT. (Moderate)
    - Strongly recommend initiating ULT for patients with frequent gout flares (>2/year) over no ULT. (High)

- Conditionally recommend initiating ULT for patients who have experienced >1 flare but have infrequent flares (≤2/year), serum uric acid (SU) >9 mg/dl, or urolithiasis. (Very low)
- Conditionally recommend against initiating any pharmacologic ULT (allopurinol, febuxostat, probenecid) for patients with asymptomatic hyperuricemia (SU >6.8 mg/dl) and no prior gout flares or subcutaneous tophi. (High)

2. Recommendations for choice of initial ULT for patients with gout
    - Strongly recommend allopurinol over all other ULTs as the preferred first-line agent for all patients, including those with CKD stage ≥3. (Moderate)
    - Strongly recommend a xanthine oxidase inhibitor over probenecid for those with CKD stage ≥3. (Moderate)
    - Strongly recommend starting allopurinol and febuxostat at a low dose with subsequent dose titration to target. (Moderate)
    - Conditionally recommend starting probenecid at a low dose (500 mg once or twice daily) with dose titration. (Moderate)
    - Strongly recommend initiating concomitant anti-inflammatory prophylaxis therapy (e.g., colchicine, nonsteroidal anti-inflammatory drugs [NSAIDs], prednisone/ prednisolone) over no anti-inflammatory prophylaxis. The choice of specific prophylaxis should consider patient factors. (Moderate)
    - Strongly recommend continuing prophylaxis for 3–6 months rather than <3 months, with ongoing evaluation and continued prophylaxis if needed for patients experiencing flares. (Moderate)
    - Conditionally recommend starting ULT during a gout flare over starting ULT after the flare has resolved. (Moderate)
    - Strongly recommend against pegloticase as first-line therapy. (Moderate)

3. Recommendations for all patients taking urate-lowering therapy (ULT)
    - Administering concomitant anti-inflammatory prophylaxis therapy (e.g., colchicine, nonsteroidal anti-inflammatory drugs [NSAIDs], prednisone/ prednisolone) over no anti-inflammatory prophylaxis therapy is strongly recommended.
    - Continuing concomitant anti-inflammatory prophylaxis therapy for 3–6 months over <3 months, with ongoing evaluation and continued prophylaxis as needed if the patient continues to experience gout flares, is strongly recommended.

Timing and Duration of ULT

- For all patients taking ULT, it is strongly recommended a treat-to-target strategy of ULT dose management that includes dose titration and subsequent dosing guided by serial SU values to achieve an SU target over a fixed, standard-dose ULT strategy. (Moderate)
- For all patients taking ULT, it is strongly recommended continuing ULT to achieve and maintain an SU target of <6 mg/dl over no target. (High)
- For all patients taking ULT, it is conditionally recommended delivery of an augmented protocol of ULT dose management by nonphysician providers to optimize the treat-to-target strategy that includes patient education, shared decision-making, and treat-to-target protocol. (Moderate)
- It is conditionally recommended continuing ULT indefinitely over stopping ULT. (Very low)

4. Recommendations for patients taking specific urate-lowering therapy (ULT) medications.

Allopurinol

- It is conditionally recommended testing HLA–B*5801 prior to starting allopurinol for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and African American patients, who have a higher prevalence of HLA–B*5801. (Very low)
- It is conditionally recommended against HLA–B*5801 testing in all others. For patients with a prior allergic response to allopurinol who cannot be treated with other oral ULT, it is conditionally recommended using allopurinol desensitization. (Very low)

Febuxostat

- For patients with gout taking febuxostat with a history of CVD or a new CV event, we conditionally recommend switching to an alternative ULT agent if available and consistent with other recommendations in this guideline. (Moderate)

Uricosurics

- For patients considered for, or taking uricosuric treatment, prior to starting any uricosuric treatment, we conditionally recommend against checking urinary uric acid over checking urinary uric acid. (Very low)
- For patients taking uricosuric treatment, we conditionally recommend against alkalinizing urine (Very low)

5. When to consider switching to a new urate-lowering therapy (ULT) strategy
    - For patients with gout taking their first XOI monotherapy at maximum-tolerated or FDA-indicated dose who are not at SU target and/or have continued frequent gout flares or nonrevolving subcutaneous tophi, it is conditionally recommended to switch the first XOI to an alternate XOI agent over adding a uricosuric agent. (Very low)
    - For patients with gout where XOI, uricosurics, and other interventions have failed to achieve SU target and who have frequent gout flares or nonresolving subcutaneous tophi, it is strongly recommended switching to pegloticase over continuing current ULT. (Moderate)
    - For patients with gout for whom XOI, uricosurics, and other interventions have failed to achieve serum urate target and who have infrequent gout flares (<2 flares/year) and no tophi, it is strongly recommended against switching to pegloticase over continuing current ULT. (Moderate)

6. Gout flare management
    - For patients experiencing a gout flare, it is strongly recommended using oral colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first-line therapy for gout flares over IL-1 inhibitors or ACTH (the choice of colchicine, NSAIDs, or glucocorticoids should be made based on patient factors and preferences). (High)
    - When colchicine is the chosen agent, it is strongly recommended low-dose colchicine over high-dose colchicine given its similar efficacy and fewer adverse effects. (High)
    - For patients experiencing gout flare for whom other anti-inflammatory therapies are poorly tolerated or contraindicated, it is conditionally recommended using IL-1 inhibition over no therapy (beyond supportive/ analgesic treatment). (Moderate)
    - For patients who may receive NPO (Nothing per mouth), it is strongly recommended glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH (Adrenocorticotropic Hormone). (High)
    - For patients experiencing gout flare, it is conditionally recommended using topical ice as an adjuvant treatment over no adjuvant treatment. (Low)

7. Management of lifestyle factors
    - For patients with gout, regardless of disease activity, it is conditionally recommended to limit alcohol intake. (Low)
    - For patients with gout, regardless of disease activity, we conditionally recommend limiting purine intake. (Low)
    - For patients with gout, regardless of disease activity, we conditionally recommend limiting high-fructose corn syrup. (Very low)
    - For overweight/obese patients with gout, regardless of disease activity, we conditionally recommend weight loss. (Very low)
    - For patients with gout, regardless of disease activity, we conditionally recommend against adding vitamin C supplementation. (Low)

8. Management of concurrent medications
    - For patients with gout, regardless of disease activity, it is conditionally recommended to switch *hydrochlorothiazide* to an alternate antihypertensive when feasible. (Very low)
    - It is conditionally recommended choosing *losartan* preferentially as an antihypertensive when feasible. (Very low)
    - It is conditionally recommended against stopping *low-dose aspirin* (in those who are taking this medication for appropriate indications). (Very low)
    - It is conditionally recommended against adding or switching to *fenofibrate*. (Very low)

1.2.2 The Italian Society of Rheumatology Clinical Practice Guidelines for the Diagnosis and Management of Gout (2019)

The Italian Society of Rheumatology Guideline's Level of evidence and recommendation grades are outlined below[9]:

Table 6. Categories of Evidence and Strengths of Recommendations Based on the Oxford Levels of Evidence

Certainty	Evidence
1	From meta-analysis of randomized controlled trials or from at least one randomized controlled trial
2	From at least one controlled study without randomization or from at least one cohort study
3	From at least one case-control study

4	From case-series or poor-quality cohort and case-control studies
5	From expert committee reports or opinions and/or clinical experience of respected authorities
Grade	**Strength**
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies or extrapolations* from level 1 studies
C	Level 4 studies or extrapolations* from level 2 or 3 studies
D	Level 5 troublingly inconsistent evidence or inconclusive studies at any level

The recommendations listed below are assigned the grades defined in the preceding table:

Diagnosis:

- For a definitive confirmation of gout, it is essential to perform identification of MSU crystals. If this is not possible, a gout diagnosis can be supported by classical clinical features such as podagra, tophi, rapid response to colchicine (2, D), and/or characteristic imaging findings (2, B). (Level 2; Strength B-D)

Assessment of co-morbidities:

- In all gout patients, it is recommended (3, C). to screen for cardiovascular risk factors and co-morbid conditions, such as cigarette smoking, hypertension, diabetes mellitus, dyslipidemia, obesity, and renal disease. Renal function and co-morbidities should be assessed at the time of diagnosis and then regularly monitored (at least annually) and appropriately managed (5, D). (Level 3-5; Strength C-D).

Timing for the treatment of acute gout:

- To provide the best care, gout attacks should be treated as soon as they occur, ideally within 24 hours of symptom onset (5, D; 1, A for colchicine). After the first gout attack, well-informed patients should be educated to self-medicate at the first warning signs and continue any established ULT (urate-lowering therapy) during an attack (5, D). (Level 1-5; Strength A-D).

First-line therapy in acute gout:

- Recommended initial options for treating acute gout flares are colchicine and/or an NSAID or COXIB. Oral corticosteroids, articular aspiration, and corticosteroid injections are also appropriate options (1, A oral; 3, C intra-articular, intramuscular). The choice of medication should be discussed with

the patient and based on the presence of co-morbidities, contraindications, and the number and type of affected joints (5, D). Initial combination therapy is an appropriate option for a severe gouty attack (5, D). (Level 1-5; Strength A-D)

Second line and adjunctive therapies in acute gout

- If the response to the first-line therapy is insufficient, switching to alternative therapy or using combination therapy is indicated (5, D). In non-responders and patients with contraindications to colchicine, NSAIDs, COXIBs, and corticosteroids (oral and injectable), IL-1 inhibitors may be considered. (1, A canakinumab; 4, D anakinra). (Level 1-5; Strength A-D)

Timing for the treatment of hyperuricemia in gout

- Patients with gout should be fully informed and involved in decisions regarding the use of ULT and when to start it (2, B). The importance of taking ULT regularly to prevent gout attacks should be explained (2, B).. ULT is recommended close to the time of first diagnosis in patients with recurrent flares, tophi, urate arthropathy and/or renal stones, or those with very high SUA levels and/or co-morbidities (renal impairment, hypertension, ischemic heart disease, heart failure) (1, A). (Level 1-5; Strength A-D)

First-line ULT in gout

- For patients with normal kidney function, allopurinol is the recommended first-line ULT (2, B). The starting dosage of allopurinol should be low (no greater than 100 mg/ day for any patient) and increased if necessary to reach the target SUA level (1, A). (Level 1-2; Strength A-B)

Second line and combination ULTs in gout

- If the SUA target cannot be achieved with an appropriate dose of allopurinol or if allopurinol is not tolerated, alternatives such as febuxostat can be considered (1, A). Uricosuric agents may be used in patients resistant to or intolerant of xanthine oxidase inhibitors (1, A). Combination therapy with a uricosuric agent and xanthine oxidase inhibitor can be used in patients not achieving the therapeutic SUA target with monotherapy (3, C). Uricase as monotherapy should be reserved for severe gout cases where other therapies have failed or are contraindicated (2, C). (Level 1-3; Strength A-C)

Flare prophylaxis

- Prophylaxis should be initiated with, or just prior to initiating, ULT and the recommended prophylactic treatment is colchicine (1, A). In patients who cannot tolerate colchicine or if colchicine is contraindicated, a low-dose NSAID or COXIB can be used as an alternative providing there are no contraindications or intolerance to NSAIDs or COXIBs (1, A). If colchicine,

NSAIDs and COXIBs are contraindicated, not tolerated, or ineffective, low dose glucocorticoids may be used (5, D). (Level 1-5; Strength A-D)

Lifestyle interventions

- Modifiable risk factors should be addressed primarily through patient education and support (2, B). Patients should be advised on a healthy lifestyle, including weight management, regular exercise, smoking cessation, limiting alcohol intake, and avoiding high-purine foods and sugar-sweetened drinks containing fructose (5, D; 2, B for dietary factors). (Level 2-5; Strength B-D)

Management points in special groups

- In patients with severe renal impairment, colchicine and NSAIDs should be avoided for acute gouty attacks. In patients with renal impairment (any grade), allopurinol may be used with dose adjustment and close monitoring for adverse events and toxicity (e.g., pruritus, rash, elevated hepatic transaminases) (4, D). If the SUA target cannot be achieved, febuxostat (2, B) is an alternative drug that can be used. With patients unable to take medicines orally, acute gouty arthritis attack may be managed by intra-articular corticosteroids, intravenous/intramuscular corticosteroids and corticotropin (2, C). In subpopulations at higher risk of severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 chronic kidney disease or worse, and Han Chinese and Thai irrespective of renal function) HLAB*5801 should be considered specifically prior to initiation (1, A). (Level 1-4; Strength A-D)

Co-prescriptions

- Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors, such as cyclosporin or clarithromycin, should be avoided (1, A). In cases of renal impairment or statin treatment, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine (2, B). If loop or thiazide diuretics are being used to treat hypertension rather than heart failure, substitution of the diuretic if possible and an alternative antihypertensive agent can be considered (4, D). (Level 1-4; Strength A-D)

Treatment of tophi

- Tophi should be treated medically by achieving a sustained reduction in SUA (2, B). Surgery is only indicated in selected cases (e.g., nerve compression, mechanical impingement, or infection) (2, B). (Level 1-2; Strength A-B)

Therapeutic targets

- The treatment target is SUA levels, eventual absence of gout attacks and resolution of tophi (2, C); monitoring should include SUA level, frequency of

gout attacks and tophi size (1, B). In all patients with gout, a SUA <6.0 mg/dl (<360 µmol/L) should be targeted and maintained life-long (1, A).

- In patients with severe gout, such as those with tophi, chronic arthropathy or frequent attacks, the target should be a SUA. <5.0 mg/dl (<300 µmol/L) (3, D). SUA level <3.0 mg/dl (180 µmol/L) is not recommended in the long term due to the possibility of adverse effects that may be associated with a very low SUA (3, D) (Level 1-3; Strength A-D).

1.2.3 Asia-Pacific League of Associations for Rheumatology Clinical Practice Guideline for Treatment of Gout (2021)

The 2021 Asia-Pacific League of Associations for Rheumatology Guideline's Level of evidence and recommendation grades are outlined below[10]:

Table 7. APLAR Strengths of Recommendations

The strength of each recommendation was classified as strong, weak, or none based on the CoE, patient values and preferences, costs, resource use, applicability, feasibility, and equity.

Recommendation	Strength
Strong	The voting panel was confident that the *benefits* from the intervention *outweigh the harm*.
Weak	The recommendation reflects the panel's reservations, which may stem from *low CoE or issues of cost, equity, applicability, or patient preferences*. Shared decision-making discussions between patients and medical practitioners would be essential for interventions with a weak recommendation.
None	The absence of strength indicates *insufficient evidence to recommend for or against a particular intervention.*

Table 8. APLAR Levels of Evidence

Level of Evidence	Definition
High	We are *very confident that the true effect is close to the estimate.*

Moderate	We have *moderate confidence in the effect estimate*: The true effect is likely to be close to this effect estimate, but there is a possibility that it is substantially different.
Low	Our *confidence in the estimate of the effect is limited*: The true effect may be substantially different from the estimate.
Very Low	We have *very little confidence* in the estimate of the effect: The true effect is likely to be substantially different from the estimate.

The recommendations listed below are assigned the grades defined in the preceding table:

Overarching principles

- Collaborative efforts among healthcare professionals and patient involvement through education and shared decision making are crucial for recognizing gout and its complications.
- A comprehensive approach to gout management involves using urate-lowering medications, making appropriate lifestyle choices, and addressing comorbidities such as cardiovascular diseases, hypertension, diabetes mellitus, metabolic syndrome, and renal disease.
- The treatment of acute gout flares requires anti-inflammatory medications and aims to prevent organ damage by reducing serum uric acid levels below its saturation point and removing monosodium urate (MSU) deposits from the body.

Asymptomatic hyperuricemia

- For patients with asymptomatic hyperuricemia (AHU) and hypertension (HTN), it is not recommended to use urate-lowering therapy (ULT) to reduce the risk of major cardiovascular events or mortality (strong recommendation, very low quality of evidence).
- For patients with AHU and chronic kidney disease (CKD), there is insufficient evidence to support or discourage the use of ULT to reduce the risk of mortality, major cardiovascular events, or prevent progression to end-stage kidney disease (no recommendation, very low quality of evidence).

Acute gout

- Among patients with acute gouty arthritis, colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), or systemic corticosteroids are recommended as first-line therapy to reduce pain (strong recommendation, moderate quality of evidence).
- A low-dose regimen of colchicine (1.5-1.8 mg/d) is preferred over a high-dose regimen (4.5-4.8 mg/d) to reduce pain in acute gouty arthritis (strong recommendation, high quality of evidence).
- There is insufficient evidence to recommend for or against the use of intra-articular corticosteroids to reduce pain in acute gouty arthritis (no recommendation, very low quality of evidence).
- Initiating ULT during an acute gout flare or after the flare in ULT-naïve patients has insufficient evidence to support either approach (no recommendation, low quality of evidence).

Prophylaxis against gout flare when initiating ULT

- Adults with gout initiating ULT should use low-dose colchicine prophylaxis (strong recommendation, low quality of evidence).
- If colchicine is intolerable or contraindicated, NSAIDs can be used as second-line prophylaxis (weak recommendation, very low quality of evidence).
- There is insufficient evidence to recommend for or against the use of systemic corticosteroids as prophylaxis (no recommendation, very low quality of evidence).

ULT

- In populations with a high (≥5%) prevalence of the HLA-B*5801 allele, testing for HLA-B*5801 before initiating allopurinol is suggested (weak recommendation, very low quality of evidence).
- There is insufficient evidence to recommend febuxostat over allopurinol among gout populations with a high prevalence of HLA-B*5801 (weak recommendation, low quality of evidence).
- Among patients newly diagnosed with gout and a serum uric acid level of ≥9 mg/dL, initiating ULT to prevent recurrence of gout flare is suggested (weak recommendation, very low quality of evidence).

Treatment of chronic tophaceous gout

- The use of a XOI (allopurinol or febuxostat) is recommended over no ULT to achieve resolution of tophi in patients with chronic tophaceous gout (strong recommendation, low quality of evidence).

- Adding lesinurad to a XOI for resolution of tophi in chronic tophaceous gout patients with serum uric acid levels >6 mg/dL is not recommended (weak recommendation, moderate quality of evidence).

Treatment of complicated gout and non-responders

- There is insufficient evidence to recommend uricosuric agent and XOI combinations other than lesinurad-allopurinol to achieve target serum uric acid levels and reduce gout flares in refractory gout patients (no recommendation, no evidence).
- Pegloticase use is suggested for refractory gout patients with contraindications or inadequate response to XOI treatment to achieve target serum uric acid levels and prevent gout flare (weak recommendation, moderate quality of evidence).

Treatment of gout with moderate to severe renal impairment

- There is insufficient evidence to recommend for or against the use of ULT to prevent CKD progression in adult patients with gout and renal impairment (no recommendation, very low quality of evidence).

NPI (Non-pharmacological interventions)

- Limiting alcohol intake to moderate amounts is suggested to prevent acute gout flare in patients with gout (weak recommendation, very low quality of evidence).
- Weight reduction interventions are suggested for overweight and obese patients with gout to prevent gout flares and lower serum uric acid levels (weak recommendation, very low quality of evidence).
- Among patients with gout, there is insufficient evidence to recommend for or against limiting purine-rich food to prevent gout flares or reduce SUA levels (no recommendation, very low quality of evidence).
- Acupuncture may be considered an option for pain relief in acute gout flare patients with intolerance or contraindications to standard anti-inflammatory medications (weak recommendation, very low quality of evidence).
- There is insufficient evidence to recommend for or against the use of herbal medicine for pain treatment in gout patients (no recommendation, very low quality of evidence).

1.2.4 Japanese Society of Gout and Uric & Nucleic Acids 2019 Guidelines for Management of Hyperuricemia and Gout (Third Edition)

The Japanese Society of Gout and Uric & Nucleic Acids 2019 Guidelines for Management of Hyperuricemia and Gout 3rd edition's Level of evidence and recommendation grades are outlined below[11]:

Table 9. Definition of Grades of Recommendation by the Japanese Society of Gout

Grade of Recommendation	Definition
High	We are *very confident that the true effect is close to the estimate.*
Moderate	We have *moderate confidence in the effect estimate*: The true effect is likely to be close to this effect estimate, but there is a possibility that it is substantially different.
Low	Our *confidence in the estimate of the effect is limited*: The true effect may be substantially different from the estimate.
Very Low	We have *very little confidence* in the estimate of the effect: The true effect is likely to be substantially different from the estimate.

The recommendations listed below are assigned the grades defined in the preceding table:

- NSAIDs, glucocorticoids, and colchicine are equally recommended for the treatment of gout attacks. The strength of evidence supporting this recommendation is moderate (Grade B).
- Lowering serum urate levels to less than 6mg/dL is recommended for the treatment of tophus. The strength of evidence supporting this recommendation is moderate (Grade B).
- Long-term colchicine cover is recommended for treating gout patients after administering urate lowering agents (ULAs) instead of using colchicine for a short period. The strength of evidence supporting this recommendation is extremely weak (Grade D).
- ULAs are partially recommended for use in hyperuricemic patients with chronic kidney disease (CKD) to help suppress the deterioration of renal function. The strength of evidence supporting this recommendation is weak (Grade C).

- ULAs are not partially recommended for use in hyperuricemic patients with hypertension to improve the prognosis and suppress cardiovascular events. The strength of evidence supporting this recommendation is weak (Grade C).
- ULAs are not partially recommended for use in hyperuricemic patients with heart failure to improve the prognosis and suppress cardiovascular events. The strength of evidence supporting this recommendation is weak (Grade C).
- Dietary education, including alcohol restriction, is recommended for managing hyperuricemia. The strength of evidence supporting this recommendation is weak (Grade C).

1.2.5 NICE Guidelines: Gout Diagnosis and Management (2022)

The NICE Guidelines for Gout diagnosis and management's Level of evidence and recommendation grades are outlined below[12]:

Table 10. Definition of Grades of Recommendation by the NICE Guidelines

Grade of Recommendation	Definition
High	We are *very confident that the true effect is close to the estimate.*
Moderate	We have *moderate confidence in the effect estimate*: The true effect is likely to be close to this effect estimate, but there is a possibility that it is substantially different.
Low	Our *confidence in the estimate of the effect is limited*: The true effect may be substantially different from the estimate.
Very Low	We have *very little confidence* in the estimate of the effect: The true effect is likely to be substantially different from the estimate.

The recommendations listed below are assigned the grades defined in the preceding table:

Symptoms and signs:

- Gout suspicion: Consider gout in individuals presenting with rapid onset of severe pain, redness, and swelling in one or both first metatarsophalangeal (MTP) joints, or the presence of tophi.
- Potential gout: Gout should be considered in individuals experiencing rapid onset of severe pain, redness, or swelling in joints other than the first MTP joints (e.g., midfoot, ankle, knee, hand, wrist, elbow).
- Differential diagnosis: Evaluate for septic arthritis, calcium pyrophosphate crystal deposition, and inflammatory arthritis in individuals with painful, red, and swollen joints.
- Urgent referral: If septic arthritis is suspected, refer the individual immediately following the local care pathway.
- Chronic gouty arthritis: Consider chronic gouty arthritis in individuals with chronic inflammatory joint pain.
- 1.1.6 Diagnostic assessment: Perform a detailed history and physical examination in individuals with suspected gout to assess symptoms and signs.

Diagnosis:

- Serum urate measurement: Confirm the clinical diagnosis of gout in individuals with symptoms and signs (as mentioned in recommendations 1.1.1 and 1.1.2) by measuring the serum urate level (serum urate level of 360 micromol/litre [6 mg/dl] or higher). If the serum urate level is below 360 micromol/litre (6 mg/dl) during a flare, and gout is strongly suspected, repeat the measurement at least 2 weeks after the flare has resolved.
- Joint aspiration and microscopy: Consider joint aspiration and microscopy of synovial fluid if the diagnosis of gout remains uncertain or unconfirmed.
- Imaging: If joint aspiration is not feasible or the diagnosis remains uncertain, consider imaging the affected joints with X-ray, ultrasound, or dual-energy CT.

Managing gout flares:

Treatment of gout flares:

- First-line treatment: Offer non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, or a short course of an oral corticosteroid for the first-line treatment of gout flares, considering the individual's comorbidities, co-prescriptions, and preferences.
- Proton pump inhibitor use: Consider adding a proton pump inhibitor for individuals with gout who are taking an NSAID to treat a gout flare.

- Alternative treatment: Consider an intra-articular or intramuscular corticosteroid injection to treat a gout flare if NSAIDs and colchicine are contraindicated, not tolerated, or ineffective.
- IL-1 inhibitor use: Do not offer an interleukin-1 (IL-1) inhibitor to treat a gout flare unless NSAIDs, colchicine, and corticosteroids are contraindicated, not tolerated, or ineffective. Refer the individual to a rheumatology service before prescribing an IL-1 inhibitor.
- Cold therapy: Advise individuals with gout that applying ice packs to the affected joint in addition to taking prescribed medicine may help alleviate pain.

Follow-up after a gout flare:

- Post-flare follow-up: Consider a follow-up appointment after a gout flare has resolved to measure the serum urate level, provide information on gout self-management and reducing the risk of future flares, assess lifestyle and comorbidities (including cardiovascular risk factors and CKD), review medications, and discuss the risks and benefits of long-term ULT.

Diet and lifestyle:

- Diet advice: Explain to individuals with gout that there is insufficient evidence to show that any specific diet prevents flares or lowers serum urate levels. Advise them to follow a healthy, balanced diet.
- Lifestyle impact: Advise individuals with gout that excess body weight or obesity, and excessive alcohol consumption, may exacerbate gout flares and symptoms.

Long-term management of gout:

Management of gout with urate-lowering therapies:

- ULT offer: Offer ULT using a treat-to-target strategy to individuals with gout who have multiple or troublesome flares, CKD stages 3 to 5, diuretic therapy, tophi, or chronic gouty arthritis.
- ULT discussion: Discuss the option of ULT using a treat-to-target strategy with individuals who have had a first or subsequent gout flare and are not within the groups listed in recommendation 1.5.1 (see recommendation 1.5.4 on when to start ULT).
- Continuation of ULT: Ensure individuals understand that ULT is usually continued after reaching the target serum urate level and is typically a lifelong treatment.
- Start ULT at least 2 to 4 weeks after a gout flare has settled. If flares are more frequent, ULT can be started during a flare (see the section on preventing flares when starting or titrating ULT).

Treat-to-target strategy

- *Start with a low dose of ULT and use monthly serum urate levels to guide dose increases*, as tolerated, until the target serum urate level is reached.

Target serum urate level

- Aim for a target serum urate level below 360 micromol/litre (6 mg/dl).
- Consider a lower target serum urate level below 300 micromol/litre (5 mg/dl) for people with gout who have tophi or chronic gouty arthritis, continue to have ongoing frequent flares despite having a serum urate level below 360 micromol/litre (6 mg/dl).

Urate-lowering therapies

- Offer either allopurinol or febuxostat as first-line treatment when starting treat-to-target ULT, taking into account the person's comorbidities and preferences.
- Offer A*llopurinol* as first-line treatment to people with gout who have major cardiovascular disease (for example, previous myocardial infarction or stroke, or unstable angina).
- Consider switching to second-line treatment with allopurinol or febuxostat if the target serum urate level is not reached or first-line treatment is not tolerated, taking into account the person's comorbidities.

Preventing gout flares when starting or titrating urate-lowering therapy

- Discuss with the person the benefits and risks of taking medicines to prevent gout flares when starting or titrating ULT.
- For people who choose to have treatment to prevent gout flares when starting or titrating ULT, offer colchicine while the target serum urate level is being reached. If colchicine is contraindicated, not tolerated or ineffective, consider a low-dose NSAID or low-dose oral corticosteroid. In June 2022, this was an off-label use of NSAIDs and oral corticosteroids.
- Consider adding a proton pump inhibitor for people with gout who are taking an NSAID or a corticosteroid to prevent gout flares when starting or titrating ULT. Take into account the person's individual risk factors for adverse events.
- Do not offer an IL-1 inhibitor when starting or titrating ULT to prevent gout flares unless colchicine, NSAIDs and corticosteroids are contraindicated, not tolerated or ineffective. Refer the person to a rheumatology service before prescribing an IL-1 inhibitor.

Monitoring serum urate level

- Consider annual monitoring of serum urate level in people with gout who are continuing ULT after reaching their target serum urate level.

1.2.6 The Hong Kong Society of Rheumatology Consensus Recommendations for the Management of Gout (2023)

The Hong Kong Society of Rheumatology consensus recommendations for the management of gout's Level of evidence and recommendation grades are outlined below[13]:

Table 11. Levels of Evidence by the Hong Kong Society of Rheumatology

Level	Type of Evidence
1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual cohort study (including low-quality RCT, e.g.,
2C	"Outcomes" research; ecological studies
3A	Systematic review (with homogeneity) of case–control studies
3B	Individual case–control study
4	Case series (and poor-quality cohort and case–control study)
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

The recommendations listed below are assigned the grades defined in the preceding table:

Overarching principles

These unifying themes include general recommendations on lifestyle and educational interventions, and the adequate management of comorbidities.

- Whenever feasible, it's important to provide education to all gout patients about the underlying mechanisms of the disease, the available treatment choices for gout-related arthritis, the accompanying medical conditions, and when to consider urate-lowering medications.
- Each individual diagnosed with gout should be given guidance by their healthcare providers on making lifestyle adjustments, highlighting the significance of such changes in effectively managing gout.
- Aside from rheumatologists, physicians who aren't specialized in rheumatology as well as general practitioners should take on the

responsibility of caring for gout patients. Nevertheless, rheumatologists should offer specialized care for those with gouty arthritis that don't respond to initial treatments or those who don't achieve treatment goals despite the proper use of urate-lowering therapy.

- Every gout patient should undergo a systematic screening process to identify any accompanying medical conditions and factors contributing to cardiovascular risk.

Acute gout management

First-line options include **colchicine**, non-steroidal anti-inflammatory drugs (**NSAIDs**), or glucocorticoids (e.g., oral, intra-articular, or intramuscular). The choice of treatment is often dependent on the patient's comorbidities and overall disease severity. Initial combination therapy may be needed for patients experiencing severe pain or attacks affecting multiple joints (Fig. 1), although the combination of an NSAID with systemic glucocorticoid is not recommended because of their additive toxicity.

- For acute gout attacks, it's crucial to initiate treatment promptly, preferably within 12 hours. Patients should be educated to self-administer medication at the initial signs of symptoms. (1B)
- As the primary approach to managing gout attacks, it's recommended to use colchicine, NSAIDs, or glucocorticoids (administered orally, intra-articularly, or intramuscularly). (1B)
- When choosing the appropriate medication(s), factors such as the presence of other health conditions, the patient's past response to treatments, the severity of the attacks, and the specific joints affected should be considered. (1B)
- As a supplementary method for alleviating pain, using topical ice is advised.
- In cases where standard treatments like colchicine, NSAIDs, and glucocorticoids are insufficient or unsuitable, IL-1 inhibitors can be considered as an option for treating gout attacks. It's important to note that IL-1 inhibitors should not be used in patients with active infections. (1B)

Gout prophylaxis

Moderate quality evidence supports the administration of agents for fare prophylaxis, mainly with colchicine, among patients being treated with ULT during the first 6 months.

- During the initiation or dosage adjustment of urate-lowering therapy (ULT), it is advisable to use colchicine at a dose of 0.5 mg once or twice daily for a period of 3 to 6 months. (2B)

- If colchicine is not well-tolerated, patients can opt for a low-dose NSAID, provided there are no medical conditions prohibiting its use. (2B)
- As an alternative option for gout prevention, IL-1 inhibitors may be considered as a secondary choice, particularly for patients who cannot take colchicine or NSAIDs due to contraindications. However, the potential costs and risks of infections associated with IL-1 inhibitors might limit their use as the initial preventive treatment. (2B)

Indications for urate-lowering therapy

Clinical trials have demonstrated that ULT is effective in treating patients with recurrent fares, tophi, urate arthropathy, and/or renal stone.

- Discussions regarding urate-lowering therapy (ULT) should take place with all individuals who have been diagnosed with gout. (5)
- Routinely suggesting ULT is not necessary for patients experiencing their initial gout attack unless they have underlying medical conditions. (5)
- ULT should be advised for all gout patients who have tophi, gout-related radiographic damage, or recurrent attacks (occurring at least 2 times annually). (1B)
- Consideration can be given to initiating ULT for gout patients following the first attack if they have experienced urolithiasis, more than one attack but with infrequent occurrences per year, or if they have renal impairment. (1B)
- For patients with gout who've encountered their first attack and possess markedly elevated serum urate levels (>0.54 mmol/L [9 mg/dL]) or have an early onset of the condition (age<40 years), the option of ULT might be considered. (1B)

Treatment target of urate-lowering therapy

There is sparse evidence from randomized trials that establishes the treat-to-target approach in gout. However, data from observational studies, including longer extension studies, appear to suggest that SUA <0.36 mmol/L (6 mg/ dL) was associated with reduced gout flares.

- Patients undergoing ULT should have their serum urate levels regularly checked and kept under 0.36 mmol/L (6 mg/dL). For individuals with tophaceous gout, a target serum urate level below 0.30 mmol/L (5 mg/dL) is advised. (3)
- Once the clinical tophi have disappeared, it's recommended to maintain the serum urate level within the range of 0.30 mmol/L (5 mg/dL) to 0.36 mmol/L (6 mg/dL). (3)

Precautions in prescribing allopurinol

The human leukocyte antigen (HLA)-B*5801 haplotype is the strongest risk factor for allopurinol-induced severe cutaneous adverse reactions (SCARs). Allopurinol-induced SCARs include drug hypersensitivity syndrome, Stevens–Johnson syndrome (SJS), and toxic epidermal necrolysis. Patients who experience SCARs after ULT often have a poor prognosis. However, there is insufficient data to establish firm recommendations for cost-effective screening in populations with low allele frequency.

- Patients who have a positive HLA-B*5801 allele test result should steer clear of using allopurinol. (2B)
- It's advisable to contemplate screening for the HLA-B*5801 allele in individuals of Asian origin like Han Chinese, Korean, Thai, as well as African American patients, and those with predisposing factors for allopurinol-induced severe cutaneous adverse reactions (SCAR), prior to initiating allopurinol treatment. These risk factors encompass patients aged 60 or above and those with renal insufficiency (chronic kidney disease stage 3 or higher). (2B)
- For patients who have previously exhibited a minor allergic reaction to allopurinol, are unable to undergo alternative urate-lowering therapy, and have received a negative HLA-B*5801 test result, the option of allopurinol desensitization could be contemplated. (5)

Use of ULT

The use of ULT for the prevention of recurrent gout fares and disease progression and the treatment of tophi is supported by clinical trials/high level of evidence. The choice between xanthine oxidase inhibitors (XOIs) and/or uricosurics is dependent on a patient’s clinical picture. These recommendations are based on a moderate to high level of evidence.

- For all individuals diagnosed with gout, a xanthine oxidase inhibitor (such as allopurinol or febuxostat) is the recommended choice of treatment. (1A)
- If allopurinol fails to attain the desired serum urate level, the option of febuxostat should be explored. Alternatively, in patients without significant kidney impairment (GFR ≥ 30 mL/min), a combination approach involving a uricosuric agent might be considered. (1A)

Co-administration of non-gout medications with ULT

- In patients with gout, calcium channel blockers and losartan are favored over alternative antihypertensive medications like loop or thiazide diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, and non-losartan angiotensin II receptor blockers. (3)

- For individuals with gout who are prescribed low-dose aspirin (<300 mg daily) either on its own or along with clopidogrel or ticagrelor for cardiovascular disease prevention or treatment, consistent monitoring of serum uric acid levels is recommended. Any necessary adjustments to urate-lowering therapy should be made based on these measurements. (5)

Lifestyle modification

Dietary interventions limiting red meat, seafood, sugary beverages, and alcohol have been the cornerstone of lifestyle management among patients who have gout. Also, moderate to heavy physical activity and overall fitness have been found to be associated with a lower incidence of gout and hyperuricemia.

- Patients should be counseled to steer clear of alcohol, fructose, sugary beverages, and to reduce their intake of dietary protein derived from meat and seafood. (2B)
- If the BMI exceeds 25 kg/m^2, it is advisable to consider weight reduction. (2B)

Section 2.0 Drug Therapy in Gout

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details other drugs that are approved for the management of gout but are not SFDA registered.

2.1 Additions

After February 2020, there have been no Gout drugs that have received FDA or EMA approval. Nevertheless, an Interleukin-1 Receptor Antagonist, Anakinra, was registered in the SFDA list and submitted to the CHI for evaluation. Hence, relevant information pertaining to this drug can be found below.

2.1.1 Anakinra

This section includes pertinent information regarding the use of Anakinra in gout[14]

Table 12. Drug Therapy with Anakinra

SCIENTIFIC NAME **Anakinra**	
SFDA Classification	Biological
SFDA Approval	Yes
US FDA	Yes, Off-label use for gout
EMA	Yes, for various inflammatory conditions

MHRA	Yes, for various inflammatory conditions
PMDA	NO
Indication (ICD-10)	M10.9
Drug Class	Antirheumatic, Disease Modifying
Drug Sub-class	Interleukin-1 Receptor Antagonist
ATC Code	L04AC03
Pharmacological Class (ASHP)	Interleukin Antagonists
DRUG INFORMATION	
Dosage Form	Solution for injection
Route of Administration	Subcutaneous Injection
Dose (Adult) [DDD]*	*SUBQ*: 100 mg once daily until symptom improvement; usual duration: 3 to 5 days. Note: Reserve use for patients in whom first-line therapies are ineffective, contraindicated, or not tolerated (Ref).
Maximum Daily Dose Adults*	100 mg/day
Dose (pediatrics)	No dosing for gout
Maximum Daily Dose Pediatrics*	No dosing for gout
Adjustment	**Dosing**: *Hepatic Impairment: Adult* There are no dosage adjustments provided in the manufacturer's labeling (has not been studied). **Dosing**: *Altered Kidney Function: Adult* CrCl ≥30 mL/minute: No dosage adjustment necessary. CrCl <30 mL/minute or end-stage renal disease: ➢ COVID-19, hospitalized patients: Consider administering 100 mg every other day for a total of 5 doses over 10 days (Ref). ➢ Other indications: Consider administering the prescribed dose every other day. Hemodialysis: Not dialyzable (<2.5%) Continuous ambulatory peritoneal dialysis (CAPD): Not dialyzable (<2.5%)

Prescribing edits*	
AGE (Age Edit): N/A	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): Anakinra should be initiated and supervised by a specialist physician in the management of gout (Rheumatologist in consultation with a clinical immunologist)	
PA (Prior Authorization): Anakinra should be given at a dose of 100 mg SC injection once per day until symptom improvement; usual duration: 3 to 5 days for patients with acute gout flares in whom first-line therapies are ineffective, contraindicated, or not tolerated (contraindications to colchicine, NSAIDs, COXIBs, and corticosteroids (oral and injectable). Anakinra should be prescribed by a specialized physician in the management of gout (Rheumatologist in consultation with a clinical immunologist) to assess CBC with differential (baseline, then monthly for 3 months, then every 3 months for a period up to 1 year); TB test (baseline); serum creatinine; signs/symptoms of infection; injection site reactions.	
QL (Quantity Limit): N/A	
ST (Step Therapy): Anakinra is used for acute gout flares for patients in whom first-line therapies are ineffective, contraindicated, or not tolerated (contraindications to colchicine, NSAIDs, COXIBs, and corticosteroids (oral and injectable)	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**<u>Most common:</u>** ***COVID-19 infection:*** • The following adverse drug reactions and incidences are derived from the FDA issued emergency use authorization (EUA [FDA 2022]). Adverse reactions reported for adults. • Hepatic: Increased gamma-glutamyl transferase, increased serum transferase ***Rheumatoid arthritis/neonatal-onset multisystem inflammatory disease (NOMAD)****:*

	The following adverse drug reactions and incidences are derived from product labeling. Adverse reactions reported for adults unless otherwise specified. • Gastrointestinal: Vomiting (infants, children, and adolescents • Immunologic: Antibody development (49%; neutralizing: 2%; no correlation between antibody development and adverse effects) • Infection: Infection (39%; serious infection: 2% to 3%; including cellulitis, pneumonia, and bone and/or joint infections) • Local: Injection site reaction (adults: 71%; infants, children, and adolescents: 16%; including bruising at injection site, erythema at injection site, inflammation at injection site, pain at injection site) • Nervous system: Headache (infants, children, adolescents, and adults: 12% to 14%) • Neuromuscular & skeletal: Arthralgia (infants, children, and adolescents: 12%) • Respiratory: Nasopharyngitis (infants, children, and adolescents: 12%) • Miscellaneous: Fever (infants, children, and adolescents: 12%) **Most serious:** • Immunologic reactions • Infectionh
Drug Interactions	**Category X:** • Abatacept • Abrocitinib • Adalimumab • Adenovirus (Types 4, 7) Vaccine

	• Anifrolumab • Baricitinib • BCG (Intravesical) • BCG Vaccine (Immunization) • Brivudine • Canakinumab • Certolizumab Pegol • Cholera Vaccine • Cladribine • Dengue Tetravalent Vaccine (Live) • Deucravacitinib • Ebola Zaire Vaccine (Live) • Etanercept • Filgotinib • Golimumab • InFLIXimab • Influenza Virus Vaccine (Live/Attenuated) • Japanese Encephalitis Virus Vaccine (Live/Attenuated) • Lenalidomide • Measles, Mumps, and Rubella Virus Vaccine • Measles, Mumps, Rubella, and Varicella Virus Vaccine • Mumps Virus Vaccine • Nadofaragene Firadenovec • Natalizumab • Pimecrolimus • Poliovirus Vaccine (Live/Bivalent/Oral) • Poliovirus Vaccine (Live/Trivalent/Oral) • Pomalidomide • Ritlecitinib • RiTUXimab • Rotavirus Vaccine • Ruxolitinib (Topical)

	• Sarilumab • Smallpox Vaccine Live • Tacrolimus (Topical) • Talimogene Laherparepvec • Tertomotide • Thalidomide • Tocilizumab • Tofacitinib • Typhoid Vaccine • Upadacitinib • Varicella Virus Vaccine • Yellow Fever Vaccine • Zoster Vaccine (Live/Attenuated) **Category D:** • Anthrax Vaccine Adsorbed • Belimumab • Coccidioides immitis Skin Test • COVID-19 Vaccine (Adenovirus Vector) • COVID-19 Vaccine (mRNA) • Denosumab • Diphtheria and Tetanus Toxoids • Diphtheria and Tetanus Toxoids, Acellular Pertussis, and Poliovirus Vaccine • Diphtheria and Tetanus Toxoids, Acellular Pertussis, Hepatitis B (Recombinant), Poliovirus (Inactivated), and Haemophilus influenzae B Conjugate (Adsorbed) Vaccine • Diphtheria and Tetanus Toxoids, Acellular Pertussis, Poliovirus and Haemophilus b Conjugate Vaccine • Diphtheria and Tetanus Toxoids, and Acellular Pertussis Vaccine • Diphtheria and Tetanus Toxoids, Whole-Cell Pertussis, Hepatitis B

	(Recombinant), and Haemophilus influenzae b Conjugate Vaccine • Diphtheria, Tetanus Toxoids, Acellular Pertussis, Hepatitis B (Recombinant), and Poliovirus (Inactivated) Vaccine • Haemophilus b Conjugate Vaccine • Hepatitis A and Hepatitis B Recombinant Vaccine • Hepatitis A Vaccine • Hepatitis B Vaccine (Recombinant [Adjuvanted]) • Hepatitis B Vaccine (Recombinant) • Hepatitis B Vaccine (Trivalent [Recombinant]) • Human Papillomavirus Vaccine (9-Valent) • Human Papillomavirus Vaccine (Bivalent) • Human Papillomavirus Vaccine (Quadrivalent) • Influenza A Virus Vaccine (H5N1) • Influenza Virus Vaccine (Inactivated) • Influenza Virus Vaccine (Recombinant) • Japanese Encephalitis Virus Vaccine (Inactivated) • Leflunomide • Meningococcal (Groups A / C / Y and W-135) Conjugate Vaccine • Meningococcal Group B Vaccine • Meningococcal Group C Conjugate Vaccine • Poliovirus Vaccine (Inactivated) • Polymethylmethacrylate • Q Fever Vaccine • Rabies Vaccine

	• Respiratory Syncytial Virus Vaccine (Recombinant [Adjuvanted]) • Respiratory Syncytial Virus Vaccine (Recombinant) • Sipuleucel-T • Smallpox and Monkeypox Vaccine (Live) • Tetanus Toxoid (Adsorbed) • Tick-Borne Encephalitis Vaccine • Travelers' Diarrhea and Cholera Vaccine • Typhoid and Hepatitis A Vaccine • Zoster Vaccine (Recombinant)
Special Population	➢ **Older adult:** Use caution due to the potential higher risk for infections. ➢ Patients with rheumatic musculoskeletal disease undergoing hip or knee replacement surgery: Hold anakinra for at least 1 day prior to surgery to reduce infection risk.
Pregnancy	• Outcome data related to the use of anakinra during pregnancy are limited. • Until additional data are available, anakinra is not currently recommended for the treatment of rheumatic and musculoskeletal diseases during pregnancy. Anakinra should be discontinued once pregnancy is confirmed. • Agents other than anakinra are currently recommended for the treatment of familial Mediterranean fever during pregnancy.
Lactation	• It is not known if anakinra is present in breast milk. • According to the manufacturer, the decision to breastfeed during therapy should consider the risk of

	infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother. Concentrations of anakinra are expected to be limited in breast milk due to large molecular weight. Also, because anakinra is unlikely to be absorbed by the infant gastrointestinal tract following exposure via breast milk, treatment with anakinra may be initiated in breastfeeding patients with rheumatic and musculoskeletal diseases.
Contraindications	Hypersensitivity to *E. coli*-derived proteins, anakinra, or any component of the formulation
Monitoring Requirements	CBC with differential (baseline, then monthly for 3 months, then every 3 months for a period up to 1 year); TB test (baseline); serum creatinine; signs/symptoms of infection; injection site reactions.
Precautions	**Immunizations**: Patients should be brought up to date with all immunizations before initiating therapy; live vaccines should not be given concurrently. There are no data available concerning the effects of therapy on vaccination or secondary transmission of live vaccines in patients receiving therapy.
Black Box Warning	N/A
REMS	N/A

HEALTH TECHONOLOGY ASSESSMENT (HTA)

Table 13. Anakinra HTA Recommendations

Medication	Agency	Date – HTA Recommendation
Anakinra	CADTH[15]	**Not available** Manufacturer Requested Reimbursement Criteria: For the treatment of Still's disease with active systemic features, in adults and pediatric patients aged 8 months and older with a body weight of 10 kg or above.
	HAS[16]	**Not available** KINERET (Anakinra) is indicated for the treatment of the signs and symptoms of rheumatoid arthritis in combination with methotrexate, in adults whose response to methotrexate alone has not been satisfactory.
	PBAC[17]	Anakinra is not PBS-subsidised for conditions other than cryopyrin associated periodic syndromes (CAPS).
	NICE[18]	**Not available**
	IQWIG[19]	**Not available**

CONCLUSION STATEMENT – ANAKINRA

Anakinra is recommended by the 2019 Italian Society of Rheumatology guidelines as second line and adjunctive therapies in acute gout flares. If the response to the first-line therapy is insufficient, switching to alternative therapy or using combination therapy is indicated (5, D). In non-responders and patients with contraindications to colchicine, NSAIDs, COXIBs, and corticosteroids (oral and injectable), IL-1 inhibitors may be considered. (1, A canakinumab; **4, D anakinra**). There is currently no data by HTA bodies to recommend the use of anakinra. For this reason, **we recommend not adding anakinra to the CHI drug formulary** until more robust data becomes available.

2.2 Modifications

Modifications have been made since February 2020.

Prescribing edits were modified to Canakinumab, Febuxostat, Colchicine and the maximum dose was modified for Colchicine and Allopurinol.

2.2.1 Canakinumab

ST: Canakinumab should be reserved for patients who have frequent flares and in whom first-line therapies are ineffective, contraindicated, or not tolerated. In patients who respond and require re-treatment, there should be an interval of at least 12 weeks before a new dose of canakinumab may be administered. FDA has approved canakinumab (Ilaris) for the treatment of gout flares in adults who cannot be treated with NSAIDs colchicine, or repeated courses of corticosteroids. The drug is also indicated for people who could not tolerate or had an inadequate response to NSAIDs or colchicine.

MD: Canakinumab should be prescribed by a specialized physician.

PA: Canakinumab should be prior authorized because it is an on-demand therapy to treat gouty arthritis attacks and caution should be exercised when administering Canakinumab to patients with infections, a history of recurring infections or underlying conditions which may predispose them to infections. Canakinumab should not be administered to patients during an active infection requiring medical intervention. Administration of Canakinumab should be discontinued if a patient develops a serious infection.

2.2.2 Febuxostat

ST: Chronic management of hyperuricemia in patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.

CU: Febuxostat should not be used concurrently with azathioprine or mercaptopurine. Febuxostat should be administered concurrently with an NSAID or colchicine (up to 6 months) to prevent gout flare, which may occur upon initiation of therapy.

MD: Febuxostat should be prescribed by rheumatologists, non- rheumatologist physicians and/or general practitioners. Risks and benefits should be considered when deciding to prescribe febuxostat or continue patients on febuxostat; Gout patients with established cardiovascular (CV) disease treated with febuxostat had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study.

AGE: Febuxostat is not recommended for use in children younger than 18 years of age.

2.2.3 Colchicine

The maximum daily dose for adults: 1.5 mg (Gout, prophylaxis during initiation of urate-lowering therapy), 6 mg (no more than 6 mg should be taken as a course of treatment)

QL: Quantity Limit added as a prescribing edit: No more than 6 mg (12 tablets) should be taken as a course of treatment. After completion of a course, another course should not be started for at least 3 days (72 hours).

2.2.4 Allopurinol

The maximum dose of Allopurinol was changed to 800 mg.

2.3 Delisting

The medications below are no longer SFDA registered[20], therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to Drugs in the disease - section 2 of CHI Gout original clinical guidance (Acemetacin was not mentioned)*

- Acemetacin

The medications below are withdrawn from the market by the European Union and FDA:

- Zurampic (Lesinurad)
  - On 31 July 2020, the European Commission issued a notification that the marketing authorization for Zurampic (lesinurad) in the European Union (EU) had been withdrawn.
  - On April 15, 2019, the FDA announced the discontinuation of Zurampic (lesinurad). The discontinuation was due to business reasons, and not due to any safety, efficacy, or quality issues. The discontinuation was effective as of February 1, 2019.
- Duzallo (Allopurinol / Lesinurad)
  - On 31 July 2020, the European Commission withdrew the marketing authorization for Duzallo (allopurinol / lesinurad) in the European Union (EU).
  - On April 15, 2019, the FDA announced the discontinuation of Ironwood Pharmaceuticals' Duzallo. (lesinurad/allopurinol) and Zurampic (lesinurad).

2.4 Other Drugs

Pegloticase, a urate-oxidase (recombinant) enzyme is used for patients with gout where XOI, uricosurics, and other interventions have failed to achieve SU target and who have frequent gout flares or non-resolving subcutaneous tophi, it is strongly recommended switching to pegloticase over continuing current ULT.

➔ *Pegloticase* is currently the only FDA-approved medication used to reduce symptoms of gout that cannot be managed by other treatments.

➔ The FDA approved *Pegloticase* (Krystexxa) injection coadministered with methotrexate.

➔ *Methotrexate* reduces the immunogenicity of *Pegloticase* and prolongs the biologic activity of *Pegloticase*.

Section 3.0 Key Recommendations Synthesis

- Strongly recommend initiating ULT for patients with 1 or more subcutaneous tophi over no ULT. (High)[8]
- Strongly recommend initiating ULT for patients with radiographic damage attributable to gout over no ULT. (Moderate)[8]
- Strongly recommend initiating ULT for patients with frequent gout flares (>2/year) over no ULT. (High)[8]
- Conditionally recommend initiating ULT for patients who have experienced >1 flare but have infrequent flares (≤2/year), serum uric acid (SU) >9 mg/dl, or urolithiasis. (Very low)[8]
- Strongly recommend allopurinol over all other ULTs as the preferred first-line agent for all patients, including those with CKD stage >3. (Moderate)[8]
- Consider switching to second-line treatment with allopurinol or febuxostat if the target serum urate level is not reached or first-line treatment is not tolerated, taking into account the person's comorbidities. (Not graded)[12]
- Strongly recommend starting allopurinol and febuxostat at a low dose with subsequent dose titration to target. (Moderate)[8]
- For patients with gout taking febuxostat with a history of CVD or a new CV event, it is conditionally recommended switching to an alternative ULT agent if available and consistent with other recommendations in this guideline. (Moderate)[8]
- Strongly recommend initiating concomitant anti-inflammatory prophylaxis therapy (e.g., colchicine, nonsteroidal anti-inflammatory drugs [NSAIDs], prednisone/ prednisolone) over no anti-inflammatory prophylaxis. The choice of specific prophylaxis should consider patient factors (Moderate)[8]
- For all patients taking ULT, it is strongly recommended continuing ULT to achieve and maintain an SU target of <6 mg/dl over no target. (High)[8]
- For patients with gout where XOI, uricosurics, and other interventions have failed to achieve SU target and who have frequent gout flares or nonresolving subcutaneous tophi, it is strongly recommended switching to pegloticase over continuing current ULT. (Moderate)[8]

- For patients experiencing a gout flare, it is strongly recommended using oral colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first-line therapy for gout flares over IL-1 inhibitors or ACTH (the choice of colchicine, NSAIDs, or glucocorticoids should be made based on patient factors and preferences). (High)[8]
- When colchicine is the chosen agent, it is strongly recommended low-dose colchicine over high-dose colchicine given its similar efficacy and fewer adverse effects. (High)[8]
- A low-dose regimen of colchicine (1.5-1.8 mg/d) is preferred over a high-dose regimen (4.5-4.8 mg/d) to reduce pain. (Strong recommendation, high quality of evidence)[10]
- For patients who may receive NPO (Nothing per mouth), it is strongly recommended glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH (Adrenocorticotropic Hormone). (High)[8]

Diagnosis:

- For a definitive confirmation of gout, it is essential to perform identification of MSU crystals. If this is not possible, a gout diagnosis can be supported by classical clinical features such as podagra, tophi, rapid response to colchicine (2, D), and/or characteristic imaging findings (2, B). (Level 2; Strength B-D)[9]

Acute gout flares

- First-line therapy

Recommended initial options for treating acute gout flares are colchicine and/or an NSAID or COXIB. Oral corticosteroids, articular aspiration, and corticosteroid injections are also appropriate options (1, A oral; 3, C intra-articular, intramuscular). The choice of medication should be discussed with the patient and based on the presence of co-morbidities, contraindications, and the number and type of affected joints (5, D). Initial combination therapy is an appropriate option for a severe gouty attack (5, D). (Level 1-5; Strength A-D)[9]

- Second line and adjunctive therapies

If the response to the first-line therapy is insufficient, switching to alternative therapy or using combination therapy is indicated (5, D). In non-responders and patients with contraindications to colchicine, NSAIDs, COXIBs, and corticosteroids (oral and injectable), IL-1 inhibitors may be considered. (1, A canakinumab; 4, D anakinra). (Level 1-5; Strength A-D)[9]

As per HTA analysis, there are no recommendations for Anakinra. (KINERET).

Gout

- First-line ULT

For patients with normal kidney function, allopurinol is the recommended first-line ULT (2, B). The starting dosage of allopurinol should be low (no greater than 100 mg/ day for any patient) and increased if necessary to reach the target SUA level (1, A). (Level 1-2; Strength A-B)[9]

- Second line and combination ULTs

- If the SUA target cannot be achieved with an appropriate dose of allopurinol or if allopurinol is not tolerated, alternatives such as febuxostat can be considered (1, A)[9]
- Uricosuric agents may be used in patients resistant to or intolerant of xanthine oxidase inhibitors (1, A)[9]
- Combination therapy with a uricosuric agent and xanthine oxidase inhibitor can be used in patients not achieving the therapeutic SUA target with monotherapy (3, C)[9]
- Uricase as monotherapy should be reserved for severe gout cases where other therapies have failed or are contraindicated (2, C)[9]

Flare prophylaxis

- Prophylaxis should be initiated with, or just prior to initiating, ULT and the recommended prophylactic treatment is colchicine (1, A)[9]
- In patients who cannot tolerate colchicine or if colchicine is contraindicated, a low-dose NSAID or COXIB can be used as an alternative providing there are no contraindications or intolerance to NSAIDs or COXIBs (1, A)[9]
- If colchicine, NSAIDs and COXIBs are contraindicated, not tolerated, or ineffective, low dose glucocorticoids may be used (5, D)[9]
- Consider adding a proton pump inhibitor for people with gout who are taking an NSAID or a corticosteroid to prevent gout flares when starting or titrating ULT. Consider the person's individual risk factors for adverse events. (Not graded)[12]

Tophi

- Tophi should be treated medically by achieving a sustained reduction in SUA (2, B)[9]
- Surgery is only indicated in selected cases (e.g., nerve compression, mechanical impingement, or infection) (2, B)[9]

Treatment of chronic tophaceous gout

- The use of a XOI (allopurinol or febuxostat) is recommended over no ULT to achieve resolution of tophi in patients with chronic tophaceous gout. (Strong recommendation, low quality of evidence)[10]
- Adding lesinurad to a XOI for resolution of tophi in chronic tophaceous gout patients with serum uric acid levels >6 mg/dL is not recommended. (Weak recommendation, moderate quality of evidence)[10]

Colchicine

- Co-prescription of colchicine with strong P-glycoprotein and/or CYP3A4 inhibitors, such as cyclosporin or clarithromycin, should be avoided (1, A)[9]
- In cases of renal impairment or statin treatment, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine (2, B)[9]
- If loop or thiazide diuretics are being used to treat hypertension rather than heart failure, substitution of the diuretic if possible and an alternative antihypertensive agent can be considered (4, D)[9]

Section 4.0 Conclusion

This report serves as an annex to the previous CHI Gout and Gouty arthritis report and aims to provide recommendations to aid in the management of Gout. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Gout. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Gout Scope

Added Sections	Rationale/Updates
2020 American College of Rheumatology Guideline for the Management of Gout[8]	➔ **Indications for pharmacologic urate-lowering therapy (ULT):** - Initiating ULT is strongly recommended for gout patients with any of the following: ≥1 subcutaneous tophi; evidence of radiographic damage (any modality) attributable to gout; OR frequent gout flares, with frequent being defined as ≥2 annually. - Initiating ULT is conditionally recommended for patients who have previously experienced >1 flare but have infrequent flares (<2/year) - Initiating ULT is conditionally recommended against in patients with gout experiencing their first gout flare. However, initiating ULT is conditionally recommended for patients with comorbid moderate to-severe CKD (stage ≥3), SU concentration >9 mg/ dl, or urolithiasis. **Indications Table 1. for ULT pharmacologic therapy** - Initiating ULT is conditionally recommended against in patients with asymptomatic hyperuricemia. ➔ **Recommendations for choice of initial ULT for patients with gout** - Treatment with allopurinol as the ***preferred first-line agent***, over all other ULTs, is strongly recommended for all patients, including those with moderate-to-severe CKD (stage ≥3) - The choice of either allopurinol or febuxostat over probenecid is strongly recommended for patients with moderate-to-severe CKD (stage ≥3) - The choice of pegloticase as a first-line therapy is strongly recommended against. - ***Starting treatment with low-dose allopurinol (≤100 mg/day and lower in patients with CKD [stage ≥3]) and febuxostat (≤40 mg/day)*** with subsequent dose titration over starting at a higher dose is strongly recommended. - Starting treatment with low-dose probenecid (500 mg once to twice daily) with subsequent dose titration over starting at a higher dose is conditionally recommended. ➔ **Recommendations for all patients taking urate-lowering therapy (ULT)**

	- **Administering concomitant anti-inflammatory prophylaxis therapy (e.g., colchicine, nonsteroidal anti-inflammatory drugs [NSAIDs], prednisone/ prednisolone) over no anti-inflammatory prophylaxis therapy is strongly recommended.** - Continuing concomitant anti-inflammatory prophylaxis therapy for 3–6 months over <3 months, with ongoing evaluation and continued prophylaxis as needed if the patient continues to experience gout flares, is strongly recommended. ➢ Timing of ULT initiation - When the decision is made that ULT is indicated while the patient is experiencing a gout flare, starting ULT during the gout flare over starting ULT after the gout flare has resolved is conditionally recommended. - A treat-to-target management strategy that includes ULT dose titration and subsequent dosing guided by serial SU measurements to achieve a target SU, over a fixed-dose ULT strategy, is strongly recommended for all patients receiving ULT. - Achieving and maintaining an SU target of <6 mg/dl over the use of no target is strongly recommended for all patients receiving ULT. - Delivery of an augmented protocol of ULT dose management by nonphysician providers to optimize the treat-to-target strategy that includes patient education, shared decision-making, and treat-to-target protocol is conditionally recommended for all patients receiving ULT. ➢ Duration of ULT - Continuing ULT indefinitely over stopping ULT is conditionally recommended. ➔ **Recommendations for patients taking specific urate-lowering therapy (ULT) medications.** *Allopurinol* ➢ Testing for the HLA–B*5801 allele prior to starting allopurinol is conditionally recommended for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and for African American patients, over not testing for the HLA–B*5801 allele. ➢ Universal testing for the HLA–B*5801 allele prior to starting allopurinol is conditionally recommended

	against in patients of other ethnic or racial background over testing for the HLA–B*5801 allele. ➢ As noted above, starting allopurinol in daily doses of ≤100 mg (and lower doses in patients with CKD) is strongly recommended over starting at a higher dose. ➢ Allopurinol desensitization is conditionally recommended for patients with a prior allergic response to allopurinol who cannot be treated with other oral ULT agents. *Febuxostat* ➢ Switching to an alternative oral ULT agent, if available and consistent with other recommendations in this guideline, is conditionally recommended for patients taking febuxostat with a history of CVD or a new CVD-related event. *Uricosurics* ➢ Checking urinary uric acid is conditionally recommended against for patients considered for or receiving uricosuric treatment. ➢ Alkalinizing the urine is conditionally recommended against for patients receiving uricosuric treatment. **9. When to consider switching to a new urate-lowering therapy (ULT) strategy** - Switching to **pegloticase** over continuing current ULT is strongly recommended for patients with gout for whom XOI treatment, uricosurics, and other interventions have failed to achieve the SU target, and who continue to have frequent gout flares (≥2 flares/year) OR who have non-resolving subcutaneous tophi. - Switching to **pegloticase** over continuing current ULT is strongly recommended against for patients with gout for whom XOI treatment, uricosurics, and other interventions have failed to achieve the SU target, but who have infrequent gout flares (<2 flares/year AND no tophi) ➔ **Gout flare management** - Using **colchicine**, **NSAIDs**, or **glucocorticoids** (oral, intraarticular, or intramuscular) as appropriate first-line therapy for gout flares over IL-1 inhibitors or adrenocorticotropic hormone (ACTH) is strongly recommended for patients experiencing a gout flare. - Given similar efficacy and a lower risk of adverse effects,

	low-dose colchicine over high-dose colchicine is strongly recommended when colchicine is the chosen age. - Using topical ice as an adjuvant treatment over no adjuvant treatment is conditionally recommended for patients experiencing a gout flare. - Using an IL-1 inhibitor over no therapy (beyond supportive/analgesic treatment) is conditionally recommended for patients experiencing a gout flare for whom the above anti-inflammatory therapies are either ineffective, poorly tolerated, or contraindicated. - Treatment with glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH is strongly recommended for patients who are unable to take oral medications. ➔ **Management of lifestyle factors** - Limiting alcohol intake is conditionally recommended for patients with gout, regardless of disease activity. - Limiting purine intake is conditionally recommended for patients with gout, regardless of disease activity. - Limiting high-fructose corn syrup intake is conditionally recommended for patients with gout, regardless of disease activity. - Using a weight loss program (no specific program endorsed) is conditionally recommended for those patients with gout who are overweight/ obese, regardless of disease activity. - Adding vitamin C supplementation is conditionally recommended against for patients with gout, regardless of disease activity. ➔ **Management of concurrent medications** - Switching hydrochlorothiazide to an alternate antihypertensive when feasible is conditionally recommended for patients with gout, regardless of disease activity. - Choosing losartan preferentially as an antihypertensive agent when feasible is conditionally recommended for patients with gout, regardless of disease activity. - Stopping low-dose aspirin (for patients taking this medication for appropriate indications) is conditionally recommended against for patients with gout, regardless of disease activity.

	Adding or switching cholesterol-lowering agents to fenofibrate is conditionally recommended against for patients with gout, regardless of disease activity.
The Italian Society of Rheumatology clinical practice guidelines for the diagnosis and management of gout[9]	**Diagnosis** Identification of MSU crystals should be performed for a definite diagnosis of gout; if not possible, a diagnosis of gout can be supported by classical clinical features such as podagra, tophi, rapid response to colchicine (2, D) and/or characteristic imaging findings (2, B). (Level 2; Strength B-D) **Assessment of co-morbidities** In all patients with gout, screening for cardiovascular risk factors and co-morbid conditions (such as cigarette smoking, hypertension, diabetes mellitus, dyslipidemia, obesity, and renal disease) is recommended (3, C). Renal function and comorbidities should be assessed at the time of diagnosis and then monitored regularly (at least annually) and managed appropriately (5, D). (Level 3-5; Strength C-D) **Timing for the treatment of acute gout** To provide optimal care, attacks should be treated as soon as an attack occurs, ideally within 24 hours of symptoms onset (5, D; 1, A for colchicine). After the first gouty attack, fully informed patients should be educated to self-medicate at the first warning symptoms and to continue any established ULT during an attack (5, D). (Level 1-5; Strength A-D) **First-line therapy in acute gout** Recommended first-line options for acute flares are colchicine and/or an NSAID or COXIB, oral corticosteroid, articular aspiration, injection of corticosteroids (1, A oral; 3, C intra-articular, intramuscular). The choice of drug(s) should be discussed with the patient and based on the presence of co-morbidities (such as impaired renal function), contraindications, the number and type of joint(s) involved (5, D). Initial combination therapy is an appropriate option for a severe gouty attack (5, D). (Level 1-5; Strength A-D) **Second-line and adjunctive therapies in acute gout** In patients with acute gout where response to an appropriate first-line therapy option is insufficient, the switch to alternative therapy or add-on combination therapy is indicated (5, D). In non-responders and in patients with contraindications to colchicine, NSAIDs, COXIBs and corticosteroid (oral and injectable), IL-1 inhibitors may be

	considered (1, A **canakinumab**; 4, D **anakinra**). (Level 1-5; Strength A-D) **Timing for the treatment of hyperuricemia in gout** Patients with gout should receive full information and be fully involved from the first presentation in decision-making concerning the use of ULT as well as to when to commence ULT (2, B). The importance of taking ULT regularly and continually to prevent the recurrence of gout attacks should be explained (2, B). ULT is indicated close to the time of first diagnosis in all patients with recurrent flares, tophi, urate arthropathy and/or renal stones, or with a very high SUA level (>8.0 mg/dL; 480 µmol/L) and/or comorbidities (renal impairment, hypertension, ischemic heart disease, heart failure) (1, A). (Level 1-5; Strength A-D) **First-line ULT in gout** In patients with normal kidney function, allopurinol is the recommended first-line ULT (2, B). Allopurinol starting dosage should be low (no greater than 100 mg/ day for any patient), and the dose then increased if required, to reach SUA target (1, A). (Level 1-2; Strength A-B) **Second-line and combination ULTs in gout** If the SUA target cannot be reached by an appropriate dose of allopurinol or allopurinol cannot be tolerated, alternatives to consider next include other XOI (febuxostat) (1, A). In patients who are resistant to, or intolerant of, XOI, uricosuric agents can be used (1, A). In patients who do not achieve a therapeutic SUA target with optimal doses of monotherapy, a uricosuric agent can be used in combination with a XOI (3, C). Uricase as monotherapy should only be considered in patients with severe gout in whom all other forms of therapy have failed or are contraindicated (2, C). (Level 1-3; Strength A-C) **Flare prophylaxis** Prophylaxis should be initiated with, or just prior to initiating, ULT and the recommended prophylactic treatment is colchicine (1, A). In patients who cannot tolerate colchicine or if colchicine is contraindicated, a low-dose NSAID or COXIB can be used as an alternative providing there are no contraindications or intolerance to NSAIDs or COXIBs (1, A). If colchicine, NSAIDs and COXIBs are contraindicated, not tolerated, or ineffective, low dose glucocorticoids may be

	used (5, D). (Level 1-5; Strength A-D) **Lifestyle interventions** Modifiable risk factors should be addressed primarily through patient education and support (2, B). Patients should be advised on a healthy lifestyle including reducing excess body weight, performing regular exercise, giving up smoking, avoiding excess alcohol, high purine foods, and sugar-sweetened drinks containing fructose (5, D; 2, B for dietary factors). (Level 2-5; Strength B-D) **Management points in special groups** In patients with severe renal impairment, colchicine and NSAIDs should be avoided for acute gouty attacks. In patients with renal impairment (any grade), allopurinol may be used with dose adjustment and close monitoring for adverse events and toxicity (e.g., pruritus, rash, elevated hepatic transaminases) (4, D). If the SUA target cannot be achieved, febuxostat (2, B) is an alternative drug that can be used. With patients unable to take medicines orally, acute gouty arthritis attack may be managed by intra-articular corticosteroids, intravenous/intramuscular corticosteroids and **corticotropin** (2, C). In subpopulations at higher risk of severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 chronic kidney disease or worse, and Han Chinese and Thai irrespective of renal function) HLAB*5801 should be considered specifically prior to initiation (1, A). (Level 1-4; Strength A-D) **Co-prescriptions** Co-prescription of **colchicine** with strong P-glycoprotein and/or CYP3A4 inhibitors, such as **cyclosporin** or **clarithromycin**, should be avoided (1, A). In cases of renal impairment or statin treatment, patients and physicians should be aware of potential neurotoxicity and/or muscular toxicity with prophylactic colchicine (2, B). If loop or thiazide diuretics are being used to treat hypertension rather than heart failure, substitution of the diuretic if possible and an alternative antihypertensive agent can be considered (4, D). (Level 1-4; Strength A-D) **Treatment of tophi** Tophi should be treated medically by achieving a sustained reduction in SUA (2, B). Surgery is only indicated in selected cases (e.g., nerve compression, mechanical impingement, or

	infection) (2, B). (Level 1-2; Strength A-B) **<u>Therapeutic targets</u>** The treatment target is SUA levels, eventual absence of gout attacks and resolution of tophi (2, C); monitoring should include SUA level, frequency of gout attacks and tophi size (1, B). In all patients with gout, a SUA <6.0 mg/dl (<360 µmol/L) should be targeted and maintained life-long (1, A). In patients with severe gout, such as those with tophi, chronic arthropathy or frequent attacks, the target should be a SUA. <5.0 mg/dl (<300 µmol/L) (3, D). SUA level <3.0 mg/dl (180 µmol/L) is not recommended in the long term due to the possibility of adverse effects that may be associated with a very low SUA (3, D). (Level 1-3; Strength A-D)
2021 Asia-Pacific League of Associations for Rheumatology clinical practice guideline for treatment of gout[10]	**Overarching principles** 1. Recognition of gout and its complications needs collaborations among physicians and allied health professionals. Further, patient education and shared decision making between physicians and patients are essential. 2. Gout management should be holistic which includes urate-lowering medications, appropriate lifestyle choices and treatment of comorbidities such as cardiovascular diseases, hypertension, diabetes mellitus, metabolic syndrome, and renal disease. 3. Treatment of acute gout flares requires anti-inflammatory medications. Treatment should also aim to prevent organ damage by removing monosodium urate (MSU) deposits from the body by lowering serum uric acid below its saturation point. 1. <u>Asymptomatic hyperuricemia</u> ➢ Among patients with asymptomatic hyperuricemia (AHU) and hypertension (HTN), we recommend against urate-lowering therapy (ULT) in patients to reduce the risk of major cardiovascular events (MACE) or mortality (cardiovascular [CV] and all-cause). (STRONG recommendation, very low CoE). ➢ Among patients with AHU and *chronic kidney disease (CKD)*, there is insufficient evidence to recommend for or against ULT to reduce the risk of mortality, MACE, or to prevent progression to end-stage kidney disease (no

	recommendation, very low CoE). 2. <u>Acute gout</u> ➢ Among patients with acute gouty arthritis, we recommend the use of colchicine, non-steroidal anti-inflammatory drugs (NSAIDs), or systemic corticosteroids as first-line therapy to reduce pain (STRONG recommendation, moderate CoE). ➢ Among patients with acute gouty arthritis, we recommend a low-dose regimen of **colchicine** (1.5-1.8 mg/d) over a high-dose regimen (4.5- 4.8 mg/d) to reduce pain (STRONG recommendation, high CoE). ➢ Among patients with acute gouty arthritis, there is insufficient evidence to recommend for or against the use of intra-articular corticoids to reduce pain (no recommendation, very low CoE) ➢ Among ULT-naïve patients with gout, there is insufficient evidence to recommend initiating ULT during acute gout flare over initiating after the flare (no recommendation, low CoE). <u>Prophylaxis against gout flare when initiating ULT.</u> ➢ Among adults with gout initiating ULT, we recommend the use of low dose colchicine prophylaxis (STRONG recommendation, low CoE) ➢ Among adults with gout initiating ULT who are intolerant or with contraindications to colchicine, we suggest NSAIDs as second-line prophylaxis (WEAK recommendation, very low CoE) ➢ Among adults with gout initiating ULT, there is insufficient evidence to recommend for or against the use of systemic corticosteroids as prophylaxis (no recommendation, very low CoE <u>ULT</u> ➢ In populations with a high (≥5%) prevalence of human leukocyte antigen (HLA)-B*5801 allele, we suggest testing for HLA-B*5801 prior to initiating allopurinol (WEAK recommendation, very low CoE) ➢ Among gout populations with high prevalence of HLA-B*5801, we neither recommend for or against **febuxostat** over **allopurinol** (WEAK recommendation, low CoE). ➢ Among patients newly diagnosed with gout and a SUA

	level of ≥9 mg/ dL, we suggest initiating ULT to prevent recurrence of gout flare (WEAK recommendation, very low CoE). 3. <u>Treatment of chronic tophaceous gout</u> ➢ Among patients with chronic tophaceous gout, we recommend the use of a XOI (**allopurinol** or **febuxostat**) over no ULT to achieve resolution of tophi (STRONG recommendation, low CoE) ➢ Among chronic tophaceous gout patients with SUA >6 mg/dL, we suggest against adding **lesinurad** to a XOI for resolution of tophi (WEAK recommendation, moderate CoE). 4. <u>Treatment of complicated gout and non-responders</u> ➢ Among adults with refractory gout, there is insufficient evidence to recommend uricosuric agent and XOI combinations other than lesinurad-allopurinol to achieve target SUA levels and reduce gout flares (no recommendation, no evidence). ➢ Among adults with refractory gout who have contraindications or inadequate response to XOI treatment, we suggest the use of pegloticase (if available) to achieve target SUA level and prevent gout flare (WEAK recommendation, moderate CoE) 5. <u>Treatment of gout with moderate to severe renal impairment</u> ➢ Among adult patients with gout and renal impairment, there is insufficient evidence to recommend for or against the use of ULT to prevent CKD progression (no recommendation, very low CoE) 6. <u>NPI</u> ➢ Among patients with gout, we suggest limiting alcohol intake to moderate amounts to prevent acute gout flare (WEAK recommendation, very low CoE). ➢ Among patients with gout, we suggest limiting alcohol intake to moderate amounts to prevent acute gout flare (WEAK recommendation, very low CoE). ➢ Among overweight and obese patients with gout, we suggest prescribing weight reduction

	interventions to prevent gout flares and lower SUA levels (WEAK recommendation, very low CoE). ➢ Among patients with acute gout flare with intolerance or contraindication to standard of care anti-inflammatory medications, acupuncture may be an option for pain relief (WEAK recommendation, very low CoE). Among adults with gout, there is insufficient evidence to recommend for or against herbal medicine in the treatment of pain (no recommendation, very low CoE)
Japanese Society of Gout and Uric & Nucleic Acids 2019 Guidelines for Management of Hyperuricemia and Gout 3rd edition [11]	1. NSAIDs, glucocorticoid and colchicine are equally recommended to be used for gout attack. Strength of evidence: B (moderate) 2. Lowering serum urate less than 6mg /dL is recommended to treat tophus. Strength of evidence: B (moderate) 3. Long term colchicine cover is recommended to treat gout patients after administration of urate lowering agents (ULAs) than short period colchicine cover. Strength of evidence: D (extremely weak) 4. ULAs are partially recommended to use for hyperuricemic patients with CKD in order to suppress the deterioration of renal function. Strength of evidence: C (weak) 5. ULAs are not partially recommended to use for hyperuricemic patients with hypertension in order to improve the prognosis and suppress the cardiovascular events. Strength of evidence: C (weak) 6. ULAs is not partially recommended to use for hyperuricemic patients with heart failure in order to improve the prognosis and to suppress the cardiovascular events. Strength of evidence: C (weak) 7. Dietary education including restriction of alcohol abuse is recommended for management of hyperuricemia. Strength of evidence: C (weak) To check the flowchart for the management of hyperuricemia and gout.
NICE Guidelines 2022, Gout diagnosis and management[12]	**Diagnosis and assessment** **<u>Symptoms and signs:</u>** 1.1.1 Suspect gout in people presenting with any of the following: • rapid onset (often overnight) of severe pain together with

	redness and swelling, in 1 or both first metatarsophalangeal (MTP) joints • tophi. 1.1.2 Consider gout in people presenting with rapid onset (often overnight) of severe pain, redness or swelling in joints other than the first MTP joints (for example, midfoot, ankle, knee, hand, wrist, elbow). 1.1.3 Assess the possibility of septic arthritis, calcium pyrophosphate crystal deposition and inflammatory arthritis in people presenting with a painful, red, swollen joint. 1.1.4 If septic arthritis is suspected, refer immediately according to the local care pathway. 1.1.5 Consider chronic gouty arthritis in people presenting with chronic inflammatory joint pain. 1.1.6 In people with suspected gout, take a detailed history and carry out a physical examination to assess the symptoms and signs. **Diagnosis**: 1.1.7 Measure the serum urate level in people with symptoms and signs of gout (see recommendations 1.1.1 and 1.1.2) to confirm the clinical diagnosis (serum urate level of 360 micromol/litre [6 mg/dl] or more). If serum urate level is below 360 micromol/litre (6 mg/dl) during a flare and gout is strongly suspected, repeat the serum urate level measurement at least 2 weeks after the flare has settled. 1.1.8 Consider joint aspiration and microscopy of synovial fluid if a diagnosis of gout remains uncertain or unconfirmed. 1.1.9 If joint aspiration cannot be carried out or the diagnosis of gout remains uncertain, consider imaging the affected joints with X-ray, ultrasound or dual-energy CT. **Managing gout flares** Treatment for gout flares: 1.3.1 Offer a non-steroidal anti-inflammatory drug (NSAID), colchicine or a short course of an oral corticosteroid for first-line treatment of a gout flare, taking into account the

	person's comorbidities, co-prescriptions and preferences. 1.3.2 Consider adding a proton pump inhibitor for people with gout who are taking an NSAID to treat a gout flare. 1.3.3 Consider an intra-articular or intramuscular corticosteroid injection to treat a gout flare if NSAIDs and colchicine are contraindicated, not tolerated or ineffective. 1.3.4 Do not offer an interleukin-1 (IL-1) inhibitor to treat a gout flare unless NSAIDs, colchicine and corticosteroids are contraindicated, not tolerated or ineffective. Refer the person to a rheumatology service before prescribing an IL-1 inhibitor. 1.3.5 Advise people with gout that applying ice packs to the affected joint (cold therapy) in addition to taking prescribed medicine may help alleviate pain. **Follow-up after a gout flare** 1.3.6 Consider a follow-up appointment after a gout flare has settled to: • measure the serum urate level • provide information about gout and how to self-manage and reduce the risk of future flares (see the section on information and support) • assess lifestyle and comorbidities (including cardiovascular risk factors and CKD) • review medications and discuss the risks and benefits of long-term ULT. **Diet and lifestyle** 1.4.1 Explain to people with gout that there is not enough evidence to show that any specific diet prevents flares or lowers serum urate levels. Advise them to follow a healthy, balanced diet. 1.4.2 Advise people with gout that excess body weight or obesity, or excessive alcohol consumption, may exacerbate gout flares and symptoms. **Long-term management of gout** <u>Management of gout with urate-lowering therapies</u> 1.5.1 Offer ULT, using a treat-to-target strategy, to people with gout who have: • multiple or troublesome flares • CKD stages 3 to 5 (glomerular filtration rate [GFR] categories G3 to G5) • diuretic therapy • tophi • chronic gouty arthritis. 1.5.2 Discuss the option of ULT, using a treat-to-target strategy, with people who have had a first or subsequent

	gout flare who are not within the groups listed in recommendation 1.5.1 (see recommendation 1.5.4 on when to start ULT). 1.5.3 Ensure people understand that ULT is usually continued after the target serum urate level is reached and is typically a lifelong treatment. 1.5.4 Start ULT at least 2 to 4 weeks after a gout flare has settled. If flares are more frequent, ULT can be started during a flare (see the section on preventing flares when starting or titrating ULT). **Treat-to-target strategy** 1.5.5 *Start with a low dose of ULT and use monthly serum urate levels to guide dose increases*, as tolerated, until the target serum urate level is reached. **Target serum urate level** 1.5.6 Aim for a target serum urate level below 360 micromol/litre (6 mg/dl). 1.5.7 Consider a lower target serum urate level below 300 micromol/litre (5 mg/dl) for people with gout who: • have tophi or chronic gouty arthritis • continue to have ongoing frequent flares despite having a serum urate level below 360 micromol/litre (6 mg/dl). **Urate-lowering therapies** 1.5.8 Offer either allopurinol or febuxostat as first-line treatment when starting treat-to-target ULT, taking into account the person's comorbidities and preferences. 1.5.9 Offer A*llopurinol* as first-line treatment to people with gout who have major cardiovascular disease (for example, previous myocardial infarction or stroke, or unstable angina). 1.5.10 Consider switching to second-line treatment with allopurinol or febuxostat if the target serum urate level is not reached or first-line treatment is not tolerated, taking into account the person's comorbidities. **Preventing gout flares when starting or titrating urate-lowering therapy** 1.5.11 Discuss with the person the benefits and risks of taking medicines to prevent gout flares when starting or titrating ULT. 1.5.12 For people who choose to have treatment to prevent gout flares when starting or titrating ULT, offer colchicine while the target serum urate level is being reached. If

	colchicine is contraindicated, not tolerated or ineffective, consider a low-dose NSAID or low-dose oral corticosteroid. In June 2022, this was an off-label use of NSAIDs and oral corticosteroids. 1.5.13 Consider adding a proton pump inhibitor for people with gout who are taking an NSAID or a corticosteroid to prevent gout flares when starting or titrating ULT. Take into account the person's individual risk factors for adverse events. 1.5.14 Do not offer an IL-1 inhibitor when starting or titrating ULT to prevent gout flares unless colchicine, NSAIDs and corticosteroids are contraindicated, not tolerated or ineffective. Refer the person to a rheumatology service before prescribing an IL-1 inhibitor. **Monitoring serum urate level** ➢ 1.5.15 Consider annual monitoring of serum urate level in people with gout who are continuing ULT after reaching their target serum urate level.

Appendix C. MeSH Terms PubMed

Query	Filters	Search Details	Results
((Gout[MeSH Terms]) OR (Gout[Title/Abstract])) OR (Gouts[Title/Abstract])	Guideline, in the last 5 years	("Gout"[MeSH Terms] OR "Gout"[Title/Abstract] OR "Gouts"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	9

Appendix D. Treatment Algorithm

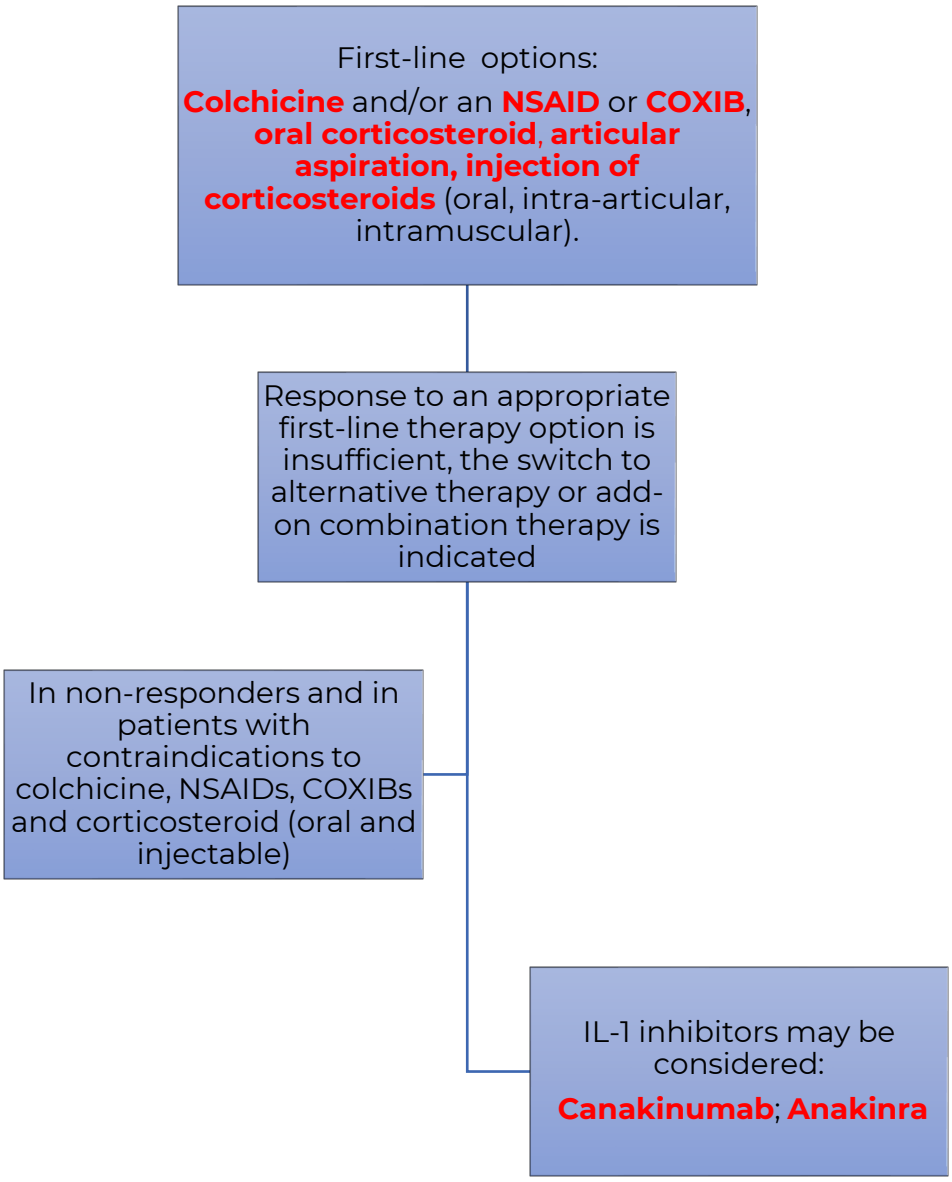

Figure 1. Acute Gout Flares Treatment

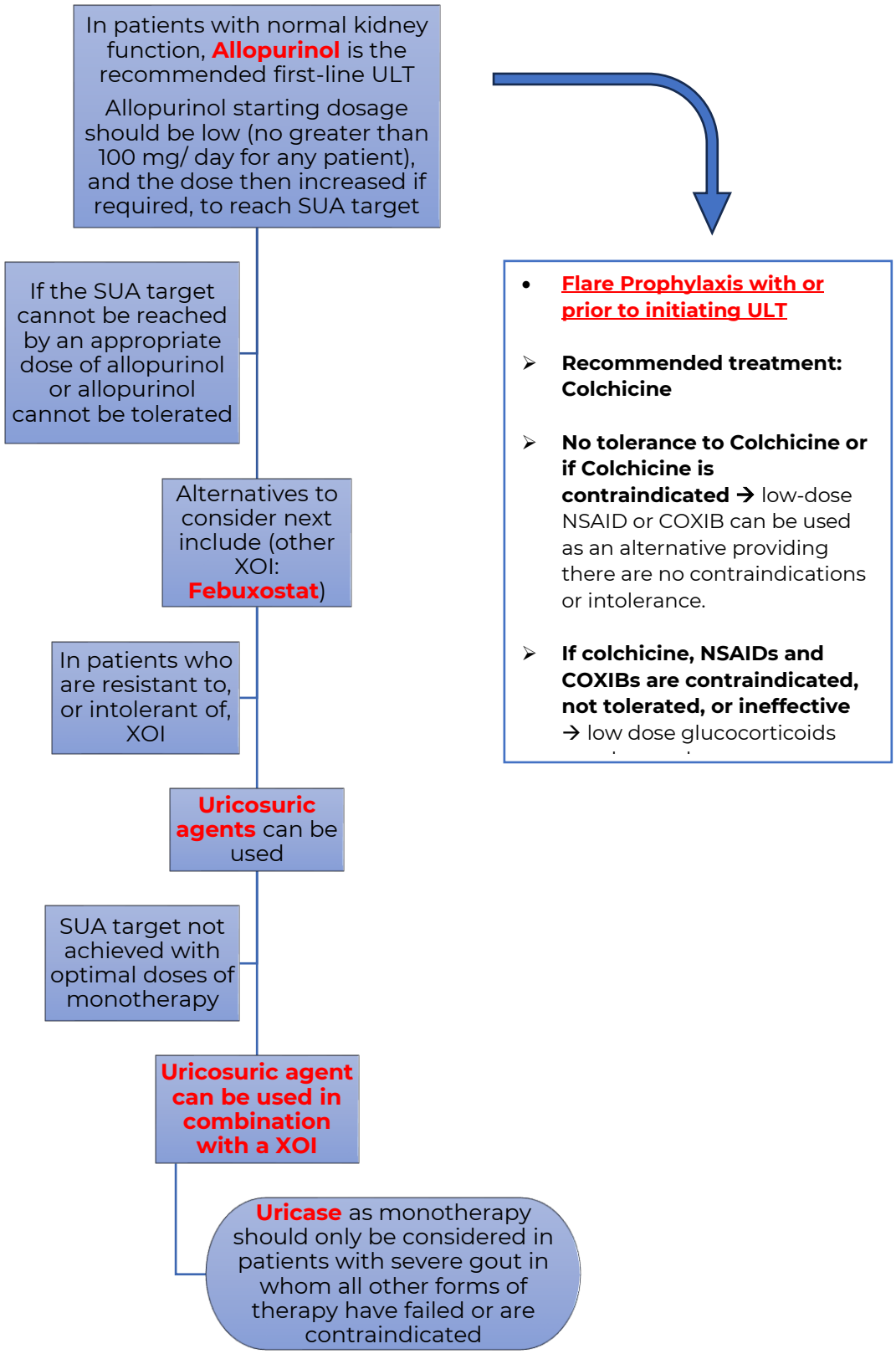

Figure 2. Gout Treatment