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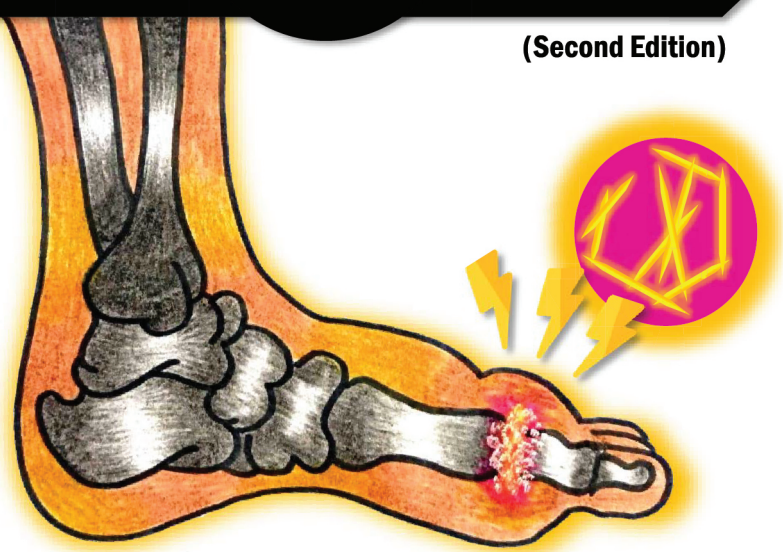
CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF GOUT

(Second Edition)



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STATEMENT OF INTENT

This clinical practice guideline (CPG) is meant to be a guide for clinical practice, based on the best available evidence at the time of development. The guideline should not override the responsibility of the practitioners to make decisions appropriate to the circumstances of the individual patient. This should be done in consultation with the patients and their families or guardians, taking into account the management options available locally.

UPDATING THE CPG

These guidelines were issued in 2021 and will be reviewed in a minimum period of four years (2025) or sooner if there is a need to do so. When it is due for updating, the Chairperson of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed. Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II-1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention; dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

FORMULATION OF RECOMMENDATION

In line with new development in CPG methodology, the CPG Unit of MaHTAS is in the process of adapting **Grading Recommendations, Assessment, Development and Evaluation (GRADE)** in its work process. The quality of each retrieved evidence and its effect size are carefully assessed/reviewed by the CPG Development Group. In formulating the recommendations, overall balances of the following aspects are considered in determining the strength of the recommendations:-

- overall quality of evidence
- balance of benefits versus harm
- values and preferences
- resource implications
- equity, feasibility and acceptability

KEY RECOMMENDATIONS

The following recommendations were highlighted by the CPG Development Group as the key clinical recommendations that should be prioritised for implementation.

Risk Factors and Preventive Strategies

- To prevent gout:
  - a healthy lifestyle should be advocated, which includes
    - maintenance of a healthy body weight
    - avoidance of alcohol
    - adherence to Dietary Approaches to Stop Hypertension (DASH) diet which
      - discourages purine-rich red meat, fructose-rich foods, full-fat dairy products and saturated fats
      - encourages vegetables, fruits, whole grains, fat-free or low-fat dairy products, fish, poultry, beans, nuts and vegetable oil
  - diuretics should be avoided if possible, or replaced by an alternative drug when used as an antihypertensive agent

Diagnosis

- Demonstration of monosodium urate (MSU) crystals in synovial fluid or tophus aspirate under polarised light microscopy should be performed to confirm the diagnosis of gout.
  - If confirmation of presence of MSU crystals is not possible, the diagnosis may be made based on typical clinical manifestations.
  - Musculoskeletal ultrasonography may assist in the diagnosis of gout with atypical presentations.

Treat-To-Target

- Treat-to-target strategy aiming for serum urate of <360 μmol/L should be applied in the treatment of all gout patients.

Treatment

- Patients with gout should be treated with urate-lowering therapy when indicated.
  - Allopurinol is the first-line therapy. It should be started at low dose and increased gradually.
  - When allopurinol is contraindicated or not tolerated, febuxostat or uricosuric agents may be considered.
- Gout flare should be treated promptly and adequately.
- In gout flare, the following monotherapy may be used:
  - colchicine
  - nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors
  - corticosteroids
- Combination of the above may be used in gout flare if response to monotherapy is insufficient.

Monitoring and Follow-up

- Monitoring of patients with gout should include:
  - clinical outcomes
  - drug-related adverse events; notably allopurinol-induced severe cutaneous adverse reaction
  - blood investigations for adverse effects of drugs
  - serum urate and comorbidity screening

Referral

- Referral of gout patients to a rheumatologist may be considered for the following:
  - diagnostic indications
    - unclear diagnosis with atypical clinical presentations including suspected gout in
      - women with onset before menopause
      - men with early onset at age <30 years without predisposing risk factors for gout
  - therapeutic indications
    - refractory to conventional therapy despite drug adherence
      - gout flare that fails to resolve despite treatment as recommended by the CPG
      - recurrent flares although SU target of <360 μmol/L is achieved
      - failure to achieve SU target of <360 μmol/L after a trial of at least three months of allopurinol at a maximally tolerated dose

        - tophaceous gout with progressive joint damage, active symptoms or growing tophi despite medical treatment
      - complicated gout with destructive joint changes
      - hypersensitivity or intolerance to allopurinol
    - special group indication
      - gout in pregnancy
- Surgical management of tophi may be considered when there is:
  - uncontrolled infection
  - entrapment neuropathy
  - risk of permanent joint damage
- Gout with urolithiasis should be assessed by a urologist.

GUIDELINES DEVELOPMENT AND OBJECTIVES

Guidelines Development

The members of the Development Group (DG) for this CPG were from the Ministry of Health (MoH), Ministry of Education and private sector. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A systematic literature search was carried out using the following electronic databases/platforms: mainly Medline via Ovid and Cochrane Database of Systemic Reviews and others e.g. Pubmed and Guidelines International Network. Refer to **Appendix 1** for **Example of Search Strategy**. The inclusion criterion was all adults with gout. The search was limited to literature published in the last 13 years, on humans and in English. In addition, the reference lists of all retrieved literature and guidelines were searched and experts in the field contacted to identify relevant studies. All searches were conducted from 12 November 2019 to 30 June 2021. Literature search was repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 30 June 2021 to be included. Future CPG updates will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

References were also made to other guidelines as listed below:

- 2020 American College of Rheumatology (ACR) Guideline for the Management of Gout
- 2016 updated European League Against Rheumatism (EULAR) evidence-based recommendations for the management of gout
- The British Society for Rheumatology (BSR) Guideline for the Management of Gout (2017)
- 2018 updated EULAR evidence-based recommendations for the diagnosis of gout
- 2012 ACR Guidelines for Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia

The CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to being used as references.

A total of 13 main clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections. Refer to **Appendix 2** for **Clinical Questions**. The DG members met 19 times throughout the development of these guidelines. All literature retrieved was appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meeting. All statements and

recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. Any differences in opinion were resolved consensually. The CPG was based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

Literature used in these guidelines were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001) while the grading of recommendation was done using the principles of GRADE (refer to page i). The writing of the CPG follows strictly the requirements of AGREE II.

On completion, the draft of the CPG was reviewed by external reviewers. It was also posted on the MoH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG and, the Health Technology Assessment (HTA) and CPG Council, MoH Malaysia, for review and approval. Details on the CPG development by MaHTAS can be obtained from Manual on Development and Implementation of Evidence-based Clinical Practice Guidelines published in 2015 (available at http://www.moh.gov.my/moh/resources/CPG_MANUAL_MAHTAS.pdf?mid=634)

OBJECTIVES

Objectives of the CPG are to provide evidence-based recommendations on management of gout in the following aspects:

- diagnosis
- prevention
- treatment
- monitoring and referral

CLINICAL QUESTIONS

Refer to **Appendix 2**.

TARGET POPULATION

Inclusion Criterion

- Adults with gout

TARGET GROUP/USER

This document is intended to guide health care providers and relevant stakeholders in primary and secondary/tertiary care in the management of gout including:

- doctors
- allied health professionals
- trainees and medical students
- policymakers
- patients and their advocates
- professional societies

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The CPG draft was reviewed by a panel of experts from both public and private sectors. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the CPG.

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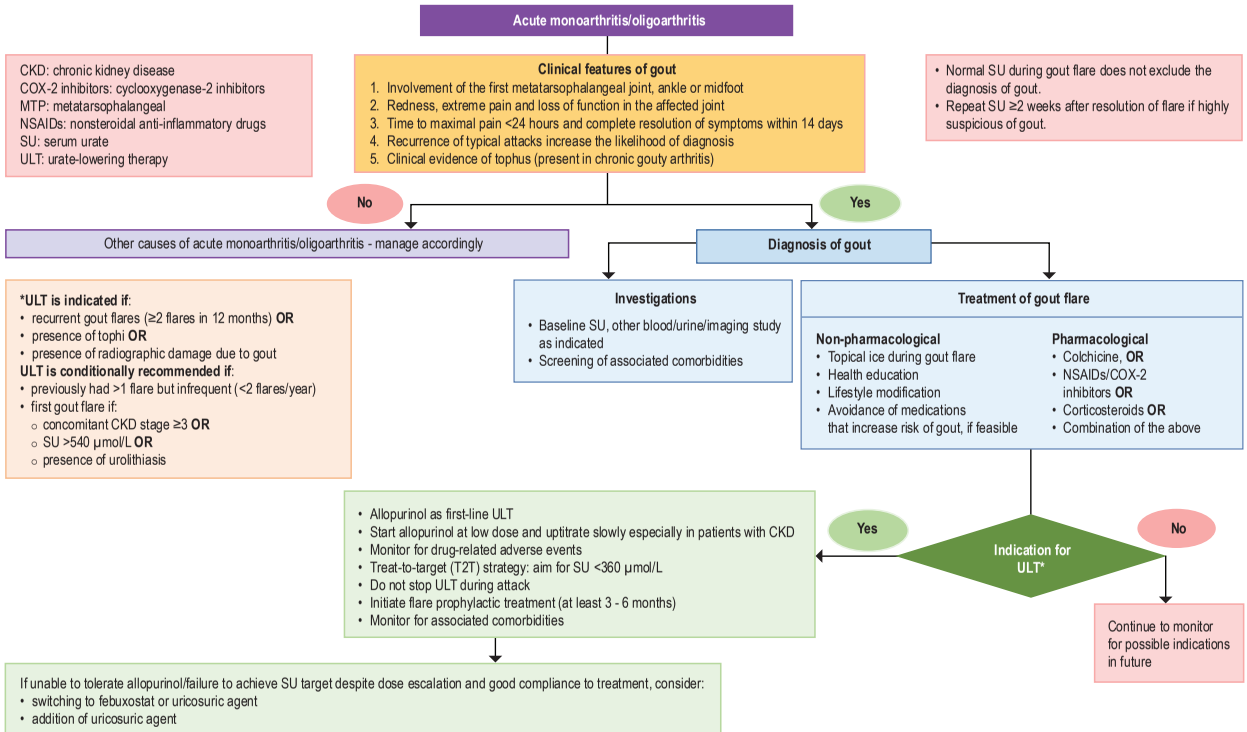
ALGORITHM ON MANAGEMENT OF GOUT



1. INTRODUCTION

The early records of gout by the Egyptians dated back to 2640 before common era (BCE). The disease was also described by Hippocrates in the fifth BCE.[1] Despite being one of the oldest joint diseases, its prevalence and incidence seem to be increasing globally.[2] Gout is associated with an increase in all-cause mortality, chronic disability, impairment of health-related quality of life, higher usage of health care services and reduced productivity.[3] In many countries, the outcomes of the disease are far from favourable due to suboptimal management. Commonly, only a third to half of patients with gout receive urate-lowering therapy (ULT) and fewer than a half of them adhere to treatment.[2] A study in a rheumatology centre in Malaysia reported that only 34.9% of its patients achieved the recommended serum urate (SU) target. Nonadherence was the main reason for failure to attain the target.[4]

The first edition of this CPG was published in 2008 by the Malaysian Society of Rheumatology. Since then, there have been advances in the understanding of the risk factors, diagnostic techniques, treatment strategy and options, and comorbidities of the disease. The employment of the treat-to-target (T2T) concept represents an important milestone in gout management. By bringing SU to <360 µmol/L, crystals are dissolved and this suggests that gout is potentially a 'curable' disease. However, ULT which is the cornerstone of therapy needs to be maintained long-term to prevent new crystal formation. The reversibility of the process is a unique feature of gout, in contrast with other rheumatic conditions. Nevertheless, if joint destruction has set in, damage is permanent.

Of equal significance is the evolving science regarding risk factors e.g. obesity and high-fructose corn syrup. Obesity is thought to be a contributing factor in the rising prevalence and incidence of gout.[2] High-fructose corn syrup increases risk of incident gout. On the other hand, plant-derived high purine diet does not.[5] Non-invasive imaging modalities e.g. ultrasound and dual-energy computed tomography (DECT) have improved the diagnostic armamentarium of gout. There is new development on the use of allopurinol. The recommendation is to 'start low, go slow' when initiating and titrating it to achieve target, especially in patients with gout and chronic kidney disease (CKD). The discovery of febuxostat, which is a non-purine xanthine oxidase inhibitor (XOI) widens the choice of ULT for prescribers. Combination therapy further expands treatment options. Last but not least, the role of education for health care professionals and patients is important too. Without proper knowledge and understanding, all the above progress will not be implemented successfully. Misconceptions and lack of knowledge of the disease among both parties are barriers to effective management of the disease.[6] Therefore an updated version of the CPG is timely.

This CPG aims to provide current concepts on the prevention, diagnosis and treatment of gout as simplified in **Algorithm** on **Management of Gout** in the preceding page. Recommendations will be based on the latest scientific evidence and availability of resources locally. It is hoped that this CPG will facilitate optimal management of gout in Malaysia. It is time to approach this ancient disease with a panoramic view and aim for SU <360 μmol/L.

2. DEFINITION AND EPIDEMIOLOGY

2.1 Definition

Gout is a disease caused by monosodium urate (MSU) crystal deposition with any of the following clinical presentations (current or prior): gout flare, chronic gouty arthritis, or subcutaneous tophus. The label 'gout' should be reserved only for clinically evident disease.[7]

Gout is a consequence of persistent hyperuricaemia.

- Not all individuals with hyperuricaemia develop MSU crystal deposition[8] or gout.[9 – 11, level II-2]

Although gout is predominantly a musculoskeletal condition with acute and chronic arthritis, as well as bursitis, it can also have extra-articular involvement e.g. chronic nephropathy and urolithiasis.

Gout, Hyperuricemia and Crystal-Associated Disease Network (G-CAN) has published a consensus on the labels and definitions of the basic elements of gout as shown below:[12, level III]

No.	Consensus Label	Consensus Definition
1.	MSU crystals	The pathogenic crystals in gout (chemical formula: $C_5H_4N_4NaO_3$)
2.	Urate	The circulating form of the final enzymatic product generated by xanthine oxidase in purine metabolism in humans (chemical formula: $C_5H_3N_4O_3^-$)
3.	Hyeruric(a)emia	Elevated blood urate concentration over the saturation threshold
4.	Gout flare	A clinically evident episode of acute inflammation induced by MSU crystals
5.	Intercritical gout	The asymptomatic period after or between gout flares, despite the persistence of MSU crystals
6.	Chronic gouty arthritis	Persistent joint inflammation induced by MSU crystals
	6a. G-CAN recommendation	The label 'chronic gout' should be avoided
7.	Tophus	An ordered structure of MSU crystals and the associated host tissue response
8.	Subcutaneous tophus	A tophus that is detectable by physical examination
9.	Imaging evidence of MSU crystal deposition	Findings that are highly suggestive of MSU crystals on an imaging test
10.	Gouty bone erosion	Evidence of a cortical break in bone suggestive of gout (overhanging edge with sclerotic margin)
11.	Podagra	A gout flare at the first metatarsophalangeal (MTP) joint

Source: Bursill D, Taylor WJ, Terkeltaub R, et al. Gout, hyperuricemia, and Crystal-Associated disease network consensus statement regarding labels and definitions for disease elements in gout. Arthritis Care Res. 2019;71(3):427-434.

2.2 Epidemiology

Globally, gout ranges from 0.1% to 6.8% in prevalence and 0.58 to 2.89 per 1,000 person-years in incidence.[2] Gout is traditionally a disease of middle-aged and older men. Its occurrence is unusual before the age of 45 years in men[13] or among premenopausal women.[14] The prevalence and incidence of gout increase with age, a pattern seen over the entire lifespan in men and after menopause in women.[2]

There are no local population-based epidemiologic studies on gout. However, hospital-based studies from a few tertiary centres in Malaysia reported a peak age of gout onset ranging from 30 to 60 years. Patients were predominantly males. They were multi-ethnic in origin and ethnicity distribution was dependent on the region where the studies were conducted. Majority of the patients were Malays in all but one study which showed a preponderance towards the Ibans.[4; 15 - 18]

3. RISK FACTORS AND PREVENTIVE STRATEGIES

The risk factors for development of gout can be categorised as modifiable and non-modifiable (refer to **Table 1** on **Risk factors for gout**). Prolonged hyperuricaemia is the major risk factor for developing gout.

3.1 Risk Factors

The table below shows the list of risk factors for gout.

Table 1. Risk factors for gout

Modifiable risk factors	
Factors that increase risk	**Factors that reduce risk**

• Obesity/overweight
• Diet
  ○ Alcohol
  ○ High-fructose corn syrup
  - Sugar-sweetened soft drinks/ beverages
  ○ Red meat
  ○ Seafood [except n-3 polyunsaturated fatty acid (PUFA)-rich fish]
• Medications*
  ○ Diuretics
  ○ Non-losartan angiotensin II receptor blockers
  ○ Angiotensin-converting enzyme (ACE) inhibitors
  ○ β-blockers
  ○ Cyclosporine
• Others
  ○ CKD
  ○ Hypertension
  ○ Psoriasis
  ○ Haematological malignancies
	• Diet
	  ○ Dairy products
	• Medications
	  ○ Losartan
	  ○ Calcium channel blockers

Non-modifiable risk factors	

• Increasing age
• Male gender
• Menopause
• Ethnicity
• Genetic
  ○ Single nucleotide polymorphism - ABCG2 gene
  ○ Enzymatic defect in purine metabolism - hypoxanthine-guanine phosphoribosyl transferase deficiency	

*The above list is not exhaustive and the decision to discontinue a medication should be made based on consideration of its benefits weighed against risks in gout patients.

a. Obesity/Overweight

Excess weight is a major risk factor for developing gout. Men with obesity may not benefit from other lifestyle modifications unless weight loss is addressed.[19, level II-2]

Individuals with body mass index (BMI) ≥30 kg/m^2 were more likely to develop gout compared with those having BMI <30 kg/m^2 (RR=2.24, 95% CI 1.76 to 2.86).[20, level II-2]

In various populations:[21, level II-2]

- 5-unit increment in BMI increased the risk of gout with RR of 1.55 (95 % CI 1.44 to 1.66)
- when compared with BMI of 20, higher BMI increased the risk of developing gout:
  - BMI 25 (RR=1.78, 95% CI 1.47 to 2.15)
  - BMI 30 (RR=2.67, 95% CI 2.16 to 3.30)
  - BMI 35 (RR=3.62, 95% CI 2.95 to 4.46)
  - BMI 40 (RR=4.64, 95% CI 3.49 to 6.18)

b. Dietary intake

- **Alcohol**

High alcohol consumption increased the risk of hyperuricaemia (OR=2.06, 95% CI 1.60 to 2.67) and gout (OR=2.58, 95% CI 1.81 to 3.66) compared with no alcohol consumption.[5, level II-2]

- **Food**

A meta-analysis showed that certain foods increased the risk of developing hyperuricaemia and gout when highest quintile intake was compared with lowest quintile intake as shown below:[5, level II-2]

Type of foods	OR for hyperuricaemia	OR for gout
Red meat	1.24 (95% CI 1.04 to 1.48)	1.29 (95% CI 1.16 to 1.44)
Seafood	1.47 (95% CI 1.16 to 1.86)	1.31 (95% CI 1.01 to 1.68)
Fructose	1.85 (95% CI 1.66 to 2.07)	2.14 (95% CI 1.65 to 2.78)

The beneficial effect of n-3 PUFA derived from fatty fish may override the potential deleterious effect of its high purine content.[22, level II-2]

Two other meta-analyses involving the same cohort studies reported by Li R et al. showed:

- high fructose consumption was associated with an increased risk of gout with RR of 1.62 (95% CI 1.28 to 2.03)[23, level II-2]
- high intake of sugar-sweetened beverages and high intake of fruit juices particularly orange juice, increased the risk of developing gout with RR of 2.08 (95% CI 1.40 to 3.08) and 1.77 (95% CI 1.20 to 2.61) respectively; however, there was no significant association between fruit intake and gout[24, level II-2]

The sweetener in both cohort studies referred to high-fructose corn syrup.

In the same meta-analysis, purine-rich vegetables or soy-based food did not increase the risk of incident gout. Dairy products were shown to lower the risk of developing hyperuricaemia (OR=0.50 95% CI 0.37 to 0.66) and/or gout (OR=0.56, 95% CI 0.44 to 0.70).[5, level II-2]

c. Medications (Antihypertensives)

In hypertensive patients, the following medications increased the risk of incident gout:[25, level II-2]

- diuretics with RR of 2.36 (95% CI 2.21 to 2.52)
- non-losartan angiotensin II receptor blockers with RR of 1.29 (95% CI 1.16 to 1.43)
- ACE inhibitors with RR of 1.24 (95% CI 1.17 to 1.32)
- β-blockers with RR of 1.48 (95% CI 1.40 to 1.57)

On the other hand, losartan and calcium channel blockers reduced the risk with RR of 0.81 (95% CI 0.70 to 0.94) and 0.87 (95% CI 0.82 to 0.93) respectively.

A recent meta-analysis also supported diuretics as a risk factor for incident gout (RR=2.39, 95% CI 1.57 to 3.65).[20, level II-2] As for effects of different classes of diuretics, a case-controlled study showed current use of loop diuretics, thiazide diuretics and thiazide-like diuretics but not potassium-sparing diuretics increased the risk of incident gout compared with past use of the medications with OR of 2.64 (95% CI 2.47 to 2.83), 1.70 (95% CI 1.62 to 1.79), 2.30 (95% CI 1.95 to 2.70) and 1.06 (95% CI 0.91 to 1.23) respectively.[26, level II-2]

d. Supplements

Vitamin C may reduce SU levels and lower the risk of gout development.

- In a study which involved various populations (postmenopausal and diabetic women, athletes, non-smoker adults, healthy male smokers etc.) with baseline SU concentrations ranging from 2.9 to 7.0 mg/dL (174 to 420 μmol/L), intake of vitamin C with median dosage of 500 mg/day reduced level of SU compared with control group (MD= -0.35 mg/dL (-21 μmol/L), 95% CI -0.66 to -0.03).[27, level I]
- Total intake of vitamin C at different doses among male health care professionals reduced the risk of incident gout compared with men with intake <250 mg/day:[28, level II-2]
  - intake of 500 to 999 mg/day (RR=0.83, 95% CI 0.71 to 0.97)
  - intake of 1000 to 1499 mg/day (RR=0.66, 95% CI 0.52 to 0.86)
  - intake of 1500 mg/day or greater (RR=0.55, 95% CI 0.38 to 0.80)

However, more evidence is warranted to conclude that vitamin C confers protection from gout.

3.2 Preventive Strategies

A large cohort study on males and predominantly white subjects with population attributable risks (PAR) as the main outcome, showed that with more preventive strategies instituted, more incident gout cases could be prevented:[19, level II-2]

- two factors in low-risk category
  - BMI <25 kg/m^2, no alcohol intake with PAR of 43% (95% CI 32 to 54)
  - BMI <25 kg/m^2, highest quintile of Dietary Approaches to Stop Hypertension (DASH) diet score with PAR of 33% (95% CI 15 to 47)
- three factors in low-risk category (BMI <25 kg/m^2, no alcohol intake, highest quintile of DASH diet score) with PAR of 69% (95% CI 47 to 82)
- four factors in low-risk category (BMI <25 kg/m^2, highest quintile of DASH diet score, no alcohol intake, no diuretic use) with PAR of 77% (95% CI 56 to 88)

Recommendation 1

- To prevent gout:
  - a healthy lifestyle should be advocated, which includes
    - maintenance of a healthy body weight
    - avoidance of alcohol
    - adherence to Dietary Approaches to Stop Hypertension (DASH) diet which
      - discourages purine-rich red meat, fructose-rich foods, full-fat dairy products and saturated fats
      - encourages vegetables, fruits, whole grains, fat-free or low-fat dairy products, fish, poultry, beans, nuts and vegetable oil
  - diuretics should be avoided if possible, or replaced by an alternative drug when used as an antihypertensive agent

- High-fructose corn syrup increases the risk of incident gout (check food label for content).

Refer to **Appendix 3** on **Alcohol Serving Size, DASH Diet Recommendations and Dietary Recommendations for Gout**.

4. NATURAL HISTORY

The natural history of untreated gout evolves through the following phases (refer to **Figure 1**):

i. asymptomatic hyperuricaemia (hyperuricaemia without gout)
ii. asymptomatic MSU crystal deposition (MSU crystal deposition without gout)
iii. recurrent gout flares with intercritical gout
iv. gout with chronic gouty arthritis/tophaceous gout/erosive gout

If untreated, gout may progress to a stage with joint damage and tophi. Gout typically presents for the first time with acute monoarthritis (first gout flare) of the first MTP joint (podagra), midfoot or ankle, and less commonly with oligoarthritis. The first gout flare is preceded by a period of asymptomatic hyperuricaemia and MSU crystal deposition. It is self-limiting and lasts about 1 - 2 weeks. This acute episode is followed by complete resolution of symptoms and signs of joint inflammation, which then enters a quiet interval called intercritical gout. If hyperuricaemia persists, the result is recurrent flares. Their occurrences gradually become more frequent and prolonged with multiple joint involvement (polyarticular gout), including those of the upper limbs. If hyperuricaemia remains uncontrolled, chronic gouty arthritis with or without tophi formation can ensue later, on an average of 10 years after initial symptom onset.

It is important to note that not all individuals with hyperuricaemia develop asymptomatic MSU crystal deposition or gout. It has yet to be elucidated that asymptomatic MSU crystal deposition will eventually lead to gout in all subjects.

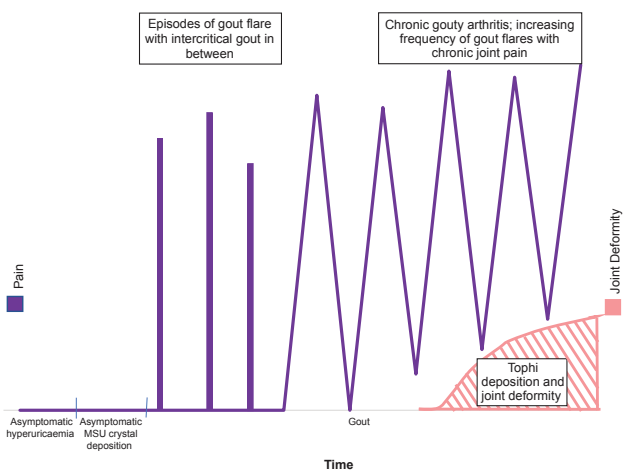


Figure 1. Natural history of gout

5. CLINICAL PRESENTATION

- The three classic clinical stages in gout are:
  - Gout flare
  - Intercritical gout
  - Chronic gouty arthritis

5.1 Gout Flare

- Defined as a clinically evident episode of acute inflammation induced by MSU crystals[12, level III]
- Presents with symptoms of acute arthritis with joint pain, swelling, warmth, redness and movement difficulty
- Occurs abruptly with joint pain peaking in intensity within 24 hours
- Can be preceded by prodromal symptoms of tingling, mild discomfort or itching in the hours leading up to an attack
- Is excruciatingly painful and usually measures >7 on a 0 - 10 Visual Analogue Scale (VAS); the pain is throbbing or burning in nature with extreme joint tenderness
- Commonest affected site is the first MTP joint; the midfoot and ankle are also commonly involved
- Usually occurs at night, with the patient's sleep interrupted due to severe joint pain
- Precipitants include acute medical or surgical illness, dehydration, alcohol and purine-rich food from animal sources
- Other than arthritis, bursitis and tendinitis, systemic features e.g. fever can be present

- **Gout flare**
  - Presents with symptoms of acute arthritis with joint pain, swelling, warmth, redness and movement difficulty
  - Occurs abruptly with joint pain peaking in intensity within 24 hours and resolves spontaneously within 1 - 2 weeks
  - Commonest affected site is the first MTP joint; the midfoot and ankle are also commonly involved joints

5.2 Intercritical Gout

- Defined as asymptomatic period after or between gout flares, despite the persistence of MSU crystals[12, level III]

5.3 Chronic Gouty Arthritis

- Defined as persistent joint inflammation induced by MSU crystals[12, level III]
- Characterised by chronic arthritis, with or without tophi, chronic joint pain, functional disability, structural joint destruction, deformity and repeated flares

Physical examination during a flare may show presence of the following:

- swelling, redness, warmth, profound tenderness with markedly reduced movement of the affected joint
- desquamation of overlying skin in superficial joints as flare resolves
- swelling, redness, warmth and tenderness of periarticular structures due to involvement of bursa or tendon
- fever

In chronic gouty arthritis, the following signs may be present:

- joint deformity e.g. fixed flexion deformity
- subcutaneous tophi (refer to **Figure 2** below)
  - appear as white or yellow, non-tender firm nodules which can be tender if inflamed
  - common sites are first MTP joint, Achilles tendon, peroneal tendon, helix of the ear, olecranon bursa and finger pad
  - may be infected with signs of inflammation
  - may ulcerate or discharge white chalky or toothpaste-like substance

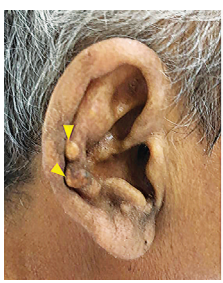


Figure 2a

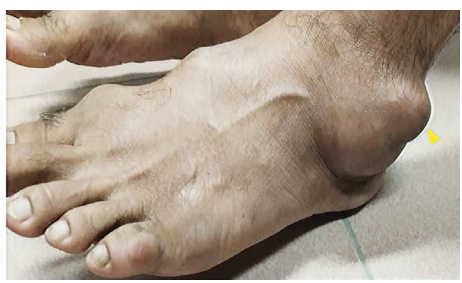


Figure 2b

Photos of tophi at antihelix of right ear (Figure 2a) and left lateral malleolus (Figure 2b) as indicated by arrows.

6. COMORBIDITIES

Comorbidities are common in people with gout which may complicate the disease management and outcomes.

A large cohort study which determined the risk of comorbidities in patients with gout compared with those without gout found:[29, level II-2]

- At the time of gout diagnosis
  - gout was associated with higher risk of at least one comorbidity listed in the Charlson index (32.25% vs 27.97%; p<0.001)
  - all cardiovascular (CV) and genitourinary diseases were associated with a higher risk of incident gout, the highest risk being for renal diseases (OR=5.96, 95% CI 5.09 to 6.98) and congestive heart disease (OR=4.37, 95% CI 4.01 to 4.76) which were diagnosed in the 10-year period before gout was diagnosed
- During follow-up after gout diagnosis
  - median time to first comorbidity in the Charlson index was 43 months (95% CI 41 to 45) in gout and 111 months (95% CI 108 to 115) in those without gout (p<0.001)
  - gout patients with a Charlson score of zero at diagnosis had higher risk of having a Charlson index ≥1 compared with those without gout with a HR of 1.41 (95% CI 1.34 to 1.48)
  - risk of developing incident comorbidities was higher in patients with gout in the following diseases:
    - congestive heart failure (HR=1.81, 95% CI 1.65 to 1.98)
    - myocardial infarction (HR=1.16, 95% CI 1.05 to 1.28)
    - hypertension (HR=1.51, 95% CI 1.43 to 1.58)
    - hyperlipidaemia (HR=1.40, 95% CI 1.31 to 1.50)
    - renal diseases (HR=3.18, 95% CI 2.88 to 3.50)
    - urolithiasis (HR=1.26, 95% CI 1.02 to 1.55)
    - chronic obstructive pulmonary disease (COPD) (HR= 1.10, 95% CI 1.02 to 1.18)
    - diabetes mellitus (HR=1.65, 95% CI 1.54 to 1.77)
    - hypothyroidism (HR=1.46, 95% CI 1.32 to 1.61)
    - liver disease (HR=1.97, 95% CI 1.61 to 2.41)
    - anaemia (HR=1.58, 95% CI 1.49 to 1.68)
- Gout was also associated with an increase in all-cause mortality (HR=1.13, 95% CI 1.08 to 1.18)

In a meta-analysis of 17 epidemiologic studies, gout was associated with both CKD (OR=2.41, 95% CI 1.86 to 3.11) and self-reported lifetime nephrolithiasis (OR=1.77, 95% CI 1.43 to 2.19).[30, level II-2]

A large population-based study demonstrated that patients with gout had an increased risk of venous thrombo-embolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE) both before and after gout diagnosis compared with the general population. The HR for VTE,

DVT and PE were 1.22 (95% CI 1.13 to 1.32), 1.28 (95% CI 1.17 to 1.41) and 1.16 (95% CI 1.05 to 1.29) respectively. Furthermore, the risk increased gradually and peaked in the year prior to diagnosis and subsequently declined progressively.[31, level II-2]

The risk of developing comorbidities was compared between patients with controlled [SU <360 μmol/L (<6.0 mg/dL)] and uncontrolled [SU ≥480 μmol/L (≥8.0 mg/dL)] gout in a large cross-sectional study. Those with uncontrolled gout were more likely to have diabetes mellitus (OR= 1.20, 95% CI 1.06 to 1.34), CKD (OR=2.04, 95% CI 1.80 to 2.30) and congestive heart failure (OR=2.65, 95% CI 2.32 to 3.01).[32, level III]

- A few large, prospective studies have shown that gout is an independent risk factor for mortality due to coronary heart disease (CHD)[33 - 35, level II-2] and kidney disease.[35, level II-2] Therefore, screening of CHD and its risk factors e.g. hypertension, diabetes mellitus, hyperlipidaemia and renal disease including urolithiasis should be done routinely.
- More evidence is warranted before recommending routine screening of diseases e.g. COPD, hypothyroidism, liver disease, anaemia and VTE.
- Patients with uncontrolled gout have a higher association with diabetes mellitus, CKD and congestive heart failure compared with well-controlled gout.

Recommendation 2

- Screening for comorbidities associated with gout e.g. hypertension, diabetes mellitus, hyperlipidaemia, coronary heart disease and renal disease including urolithiasis should be done upon diagnosis and during follow-up.

7. DIAGNOSIS

Demonstration of MSU crystals in synovial fluid (SF) or tophus aspirate confirms the diagnosis of gout. If confirmation is not possible, diagnosis of gout can be made through the evaluation of clinical manifestations, laboratory investigations and imaging modalities.

7.1 Demonstration of Monosodium Urate Crystals in Synovial Fluid or Tophus Aspirate

Demonstration of MSU (negative birefringent) crystals in SF or tophus aspirate is the gold standard for the diagnosis of gout (**Figure 3**). It has 100% specificity. Polarised light microscopy is the standard method for detecting MSU crystals. Low-quality evidence suggested that MSU crystals remained stable in SF stored at room temperature for 24 - 48 hours and should be refrigerated (at 4ºCelcius) if analysis was to be delayed.[36, level III]

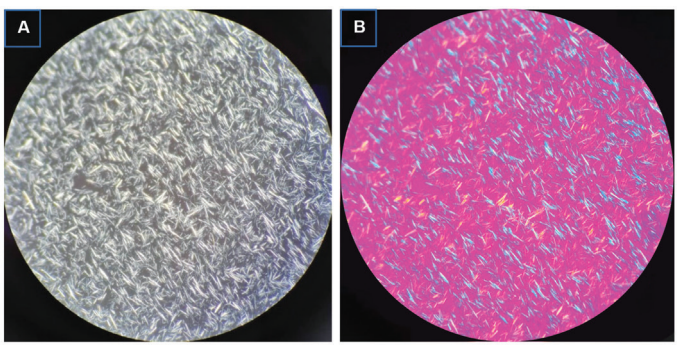


Figure 3. Photos of needle-shaped MSU crystals in SF viewed through A) dark-field microscopy B) polarised light microscopy

7.2 Clinical Manifestations

A systematic review of moderate-quality papers showed that presence of tophus and response to colchicine had high specificity of 1.00 (95% CI 0.97 to 1.00) and 0.85 (95% CI 0.55 to 0.98) respectively when compared with MSU crystal demonstration in the diagnosis of gout.[37, level III]

Clinical features of gout are described in **Chapter 4** on **Natural History** and **Chapter 5** on **Clinical Presentation**.

7.3 Laboratory Investigations

Epidemiological studies have shown that not all hyperuricaemic subjects develop gout as discussed below.

The risks of both gout incidence in gout-free individuals and recurrence of flares in individuals with preexisting gout increase with higher SU levels at baseline.[38, level II-2]

In a meta-analysis of four cohort studies with a mean follow-up of 11.2 years, higher SU levels at baseline were associated with an increased risk of developing gout (dose-dependent) compared with baseline SU <6 mg/dL (360 μmol/L):[9, level II-2]

- 6.0 - 6.9 mg/dL (360 - 414 μmol/L) with HR of 2.69 (95% CI 2.03 to 3.57)
- 7.0 - 7.9 mg/dL (420 - 474 μmol/L) with HR of 6.64 (95% CI 5.04 to 8.77)
- 8.0 - 8.9 mg/dL (480 - 534 μmol/L) with HR of 14.92 (95% CI 11.06 to 20.13)
- 9.0 - 9.9 mg/dL (540 - 594 μmol/L) with HR of 29.66 (95% CI 20.79 to 42.31)
- ≥10 mg/dL (≥600 μmol/L) with HR of 63.96 (95% CI 42.54 to 96.16)

- Diagnosis of gout should not be made based on hyperuricaemia alone.
- The cut-off SU level to diagnose hyperuricaemia based on urate saturation threshold is a SU concentration of >6.8 mg/dL (408 μmol/L) at physiological pH and body temperature.[39]
- A normal or low SU during flare does not exclude gout, as the level may not be elevated during a flare. If clinical suspicion of gout is high, SU may be repeated two weeks or more after complete resolution of flare.

7.4 Imaging Modalities

a. Plain radiography

Changes in plain radiograph take several years to develop. Thus, utility of plain radiograph is limited in early gout but may be helpful in supporting the diagnosis in later stages.

Typical radiographic features of established gout include (refer to **Figure 4**):

- bone erosions with overhanging edges and a sclerotic rim (A)
- bone proliferation (B)
- joint space narrowing (C)
- soft tissue masses (tophi), which can be calcified (D)

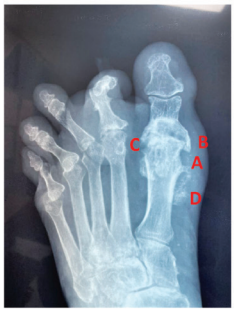


Figure 4a. AP radiograph of left foot
AP = anteroposterior

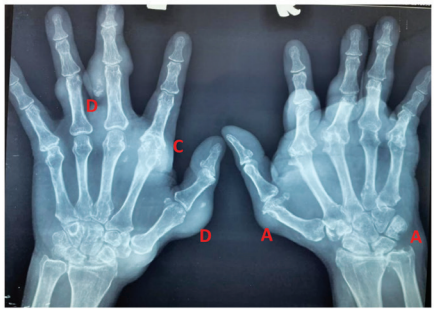


Figure 4b. AP radiograph of both hands

b. Ultrasonography

Musculoskeletal ultrasonography is useful in assisting the diagnosis of gout especially when the presentation is atypical and microscopic demonstration of MSU crystals is not feasible. Evidence supporting its diagnostic utility is described as follows:

- In a systematic review, ultrasound findings of double contour sign (DCS), tophi, punctiform deposits in synovial membrane and hyperechoic spots in SF showed good specificity ranging from 0.65 to 1.00 for diagnosis of gout with MSU identification as the reference standard.[37, level III]
- A meta-analysis of three diagnostic studies on ultrasound in joint/location-based evaluations for the diagnosis of gout gave a sensitivity of 0.71 (95% CI 0.64 to 0.78), specificity of 0.62 (95% CI 0.56 to 0.67) and AUC of 0.8549 for DCS.[40, level III]

The DCS is indicated by arrow heads as shown in **Figures 5a** and **5b**.

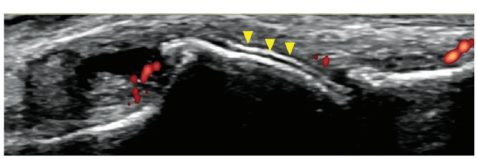


Figure 5a. Longitudinal ultrasound scan of left first MTP joint

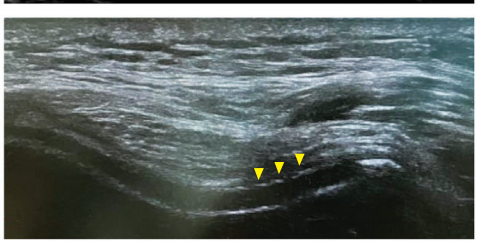


Figure 5b. Suprapatellar transverse ultrasound scan of right knee joint

c. Dual-energy Computed Tomography

A good meta-analysis of seven studies showed that DECT had a high sensitivity of 88% (95% CI 84 to 90), specificity of 90% (95% CI 85 to 93) and AUC of 0.9565 as a tool for the diagnosis of gout.[41, level III] However, this imaging modality is not utilised as a diagnostic tool for gout as it is not widely available in Malaysia.

7.5 Classification Criteria

ACR-EULAR 2015 Gout Classification Criteria was originally developed for the purpose of research. It incorporates clinical, laboratory and radiology features/modalities in diagnosing gout. A person with a score ≥8 can be classified as having gout with a sensitivity of 92% and specificity of 89%. The criteria can also be used for gout classification based on only clinical features and SU level. In this setting, it has a sensitivity of 85% and specificity of 78%. Although regarded as classification criteria, it can also be applied in daily clinical practice for the diagnosis of gout. Refer to Table 2 below for the classification. An electronic calculator is now available at:
http://goutclassificationcalculator.auckland.ac.nz
https://www.mdcalc.com/acr-eular-gout-classification-criteria

Table 2. The ACR/EULAR gout classification criteria

	Categories	Score
Step 1: Entry criterion (only apply criteria below to those meeting this entry criterion)	At least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa	
Step 2: Sufficient criterion (if met, can classify as gout without applying criteria below)	Presence of MSU crystals in a symptomatic joint or bursa (i.e., in synovial fluid) or tophus	
Step 3: Criteria (to be used if sufficient criterion not met)		
Clinical		
Pattern of joint/bursa involvement during symptomatic episode(s) ever*	Ankle or midfoot (as part of monoarticular or oligoarticular episode without involvement of the first metatarsophalangeal joint)	1
	Involvement of the first metatarsophalangeal joint (as part of monoarticular or oligoarticular episode)	2
Characteristics of symptomatic episode(s) ever • Erythema overlying affected joint (patient-reported or physician-observed) • Can't bear touch or pressure to affected joint • Great difficulty with walking or inability to use affected joint	One characteristic Two characteristics Three characteristics	1 2 3
Time course of episode(s) ever Presence (ever) of ≥2, irrespective of anti-inflammatory treatment: • Time to maximal pain <24 hours • Resolution of symptoms in ≤14 days • Complete resolution (to baseline level) between symptomatic episodes	One typical episode Recurrent typical episodes	1 2
Clinical evidence of tophus Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (e.g. Achilles)	Present	4
Laboratory		
Serum urate: Measured by uricase method. Ideally should be scored at a time when the patient was not receiving ULT and it was >4 weeks from the start of an episode (i.e. during intercritical period); if practicable, retest under those conditions. The highest value irrespective of timing should be scored.	<4 mg/dL (<0.24 mmol/L)** 6 - <8 mg/dL (0.36 - <0.48 mmol/L) 8 - <10 mg/dL (0.48 - <0.60 mmol/L) ≥ 10 mg/dL (≥0.60 mmol/L)	-4 2 3 4
Synovial fluid analysis of a symptomatic (ever) joint or bursa (should be assessed by a trained observer)***	MSU negative	-2
Imaging[$]		
Imaging evidence of urate deposition in symptomatic (ever) joint or bursa: Ultrasound evidence of double contour sign[#] *or* DECT demonstrating urate deposition[¥]	Present (either modality)	4
Imaging evidence of gout-related joint damage: Conventional radiography of the hands and/or feet demonstrates at least 1 erosion[€]	Present	4

*Symptomatic episodes are periods of symptoms that include any swelling, pain, and/or tenderness in a peripheral joint or bursa.
**If serum urate level is <4 mg/dL (<0.24 mmol/L), *subtract 4 points*; if serum urate level is ≥4 -<6 mg/dL (≥0.24 -<0.36 mmol/L), score this item as 0.
***If polarising microscopy of synovial fluid from a symptomatic (ever) joint or bursa by a trained examiner fails to show monosodium urate monohydrate (MSU) crystals, *subtract 2 points*. If synovial fluid was not assessed, score this item as 0.
$If imaging is not available, score these items as 0.
#Hyperechoic irregular enhancement over the surface of the hyaline cartilage that is independent of the insonation angle of the ultrasound beam (note: false-positive double contour sign [artifact] may appear at the cartilage surface but should disappear with a change in the insonation angle of the probe).
¥Presence of colour-coded urate at articular or periarticular sites. Images should be acquired using a dual-energy computed tomography (DECT) scanner, with data acquired at 80 kV and 140 kV and analysed using gout-specific software with a 2-material decomposition algorithm that colour-codes urate. A positive scan is defined as the presence of colour-coded urate at articular or periarticular sites. Nailbed, submillimeter, skin, motion, beam hardening, and vascular artifacts should not be interpreted as DECT evidence of urate deposition.
€Erosion is defined as a cortical break with sclerotic margin and overhanging edge, excluding distal interphalangeal joints and gull wing appearance.

Reference: Neogi T, Jansen TL, Dalbeth N, et al. 2015 Gout Classification Criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheumatol. 2015;67(10):2557-2568.

In conclusion, diagnosis of gout should ideally be confirmed by the presence of MSU crystals. However, if demonstration of MSU crystals is not possible, gout can be diagnosed based on typical clinical manifestations. This is supported by the presence of hyperuricaemia. Plain radiography is helpful only in later part of the disease. Musculoskeletal ultrasonography maybe useful in atypical presentations.

Recommendation 3

- Demonstration of monosodium urate (MSU) crystals in synovial fluid or tophus aspirate under polarised light microscopy should be performed to confirm the diagnosis of gout.
  - If confirmation of the presence of MSU crystals is not possible, the diagnosis may be made based on typical clinical manifestations.
  - Musculoskeletal ultrasonography may assist in the diagnosis of gout with atypical presentations.

8. BASELINE INVESTIGATIONS

Baseline investigations are performed to support the diagnosis of gout and identify comorbidities associated with gout and those that may influence treatment decisions. Refer to **Table 3** on **Baseline investigations in gout**.

Table 3. Baseline investigations in gout

Investigations	Rationale
Full blood count (FBC)	To exclude infection or lymphoproliferative/ myeloproliferative disorders
Renal profile (RP)	To exclude renal disease leading to hyperuricaemia, renal disease secondary to chronic nephropathy, urolithiasis
Liver function test (LFT)	Baseline prior to commencement of treatment
SU	Presence of hyperuricaemia is supportive of gout
Fasting blood sugar (FBS)	To detect the presence of diabetes/insulin resistance
Fasting serum lipid (FSL)	To detect hyperlipidaemia
Full and microscopic examination of urine (Urine FEME)	Presence of blood and/or protein may suggest renal disorders
Plain radiography of affected joint(s)	To detect abnormalities caused by gout
Ultrasound of the kidneys, ureters and bladder (USG KUB)	To detect urolithiasis or renal parenchymal disease
Electrocardiogram (ECG)	To detect CHD

9. DIFFERENTIAL DIAGNOSES

Gout usually presents with acute monoarthritis and less commonly with oligoarthritis. A diagnosis of gout can be reasonably made in a hyperuricaemic patient who presents with acute monoarthritis of the first MTP joint. However, other causes of acute monoarthritis/oligoarthritis should be considered before making a diagnosis of gout.

The main differential diagnoses of gout and their supportive features are:

i. septic arthritis (key differential diagnosis)
   - commonly involves knee joint (other sites are hip, shoulder, ankle, wrist)
   - acutely painful/tender, hot, swollen, erythematous and immobile joint
   - presence of systemic features e.g. fever, ill or septic-looking
   - risk factors e.g. concomitant bacteraemia, recent intra-articular injection
   - leukocytosis and raised C-reactive protein

ii. acute calcium pyrophosphate crystal arthritis
   - age >60 years old
   - involvement of a degenerative joint
   - radiography of affected joint may show presence of chondrocalcinosis

iii. psoriatic arthritis
   - presence of psoriasis, nail dystrophy (e.g. pitting, onycholysis or crumbling)

iv. reactive arthritis
   - recent genitourinary or gastrointestinal (GI) infection
   - presence of urethral discharge or ulcer, rash on soles, conjunctivitis

10. ASYMPTOMATIC HYPERURICAEMIA

Treatment of asymptomatic hyperuricaemia with ULT to prevent gout has been a much debated topic for decades. There is also emerging interest in the role of ULT in preventing progression of disease in CKD or CV events.

a. Urate-lowering therapy for gout prevention in asymptomatic hyperuricaemia

A cohort study showed that not all patients with hyperuricaemia will develop gout. Only 22% of patients with SU >9.0 mg/dL (540 µmol/L) will do so in five years.[11, level II-2] Two more recent studies showed similar results with the following findings:

- the absolute risks of developing incident gout over 30 years with SU >405 µmol/L at baseline, were 13.3% (95% CI 12.2 to 14.8) in men and 17.7% (95% CI 12.4 to 24.6) in women, respectively[9, level II-2]
- 15-year cumulative incidence of gout ranged from 1.12% (95% CI 0.90 to 1.35) for baseline SU <6 mg/dL (360 µmol/L) to 48.57% (95% CI 30.50 to 66.64) for baseline SU ≥10 mg/dL (600 µmol/L)[10, level II-2]

In an RCT on patients with CKD stage 3 and asymptomatic hyperuricaemia, the incidence of gouty arthritis was lower in febuxostat compared with placebo (p=0.007). However, the incidence rates of gouty arthritis in both groups were low (0.91% and 5.86% for febuxostat and placebo respectively).[42, level I] Therefore, the benefit of starting ULT may not outweigh the potential adverse events (AE) of treatment as the vast majority of these patients will not develop gout.

b. Urate-lowering therapy for renoprotective effect in asymptomatic hyperuricaemia

Hyperuricaemia is associated with progression of CKD. However, direct causality between them is not well established as it is unclear whether high SU is a cause of kidney disease or just a common co-occurrence.

In a meta-analysis of five RCTs comparing allopurinol with controls (placebo or colchicine) in a heterogenous population of CKD patients (hyperuricaemic and non-hyperuricaemic), there was no significant difference in the change of glomerular filtration rate (GFR) from baseline between the two groups. However, meta-analysis of three other RCTs with serum creatinine as study end point showed that change in serum creatinine concentration from baseline was in favour of allopurinol (MD= -0.4 mg/dL, 95% CI -0.8 to -0.0). The quality of the primary papers included was moderate.[43, level I]

An RCT involving type 1 diabetic patients with kidney disease (mean SU of 360 µmol/L) also revealed no significant difference in the decline

of iohexol-based GFR between the allopurinol and placebo groups after three years of treatment.[44, level I] The quality of the RCT was moderate.

In one RCT among CKD stage 3 patients and asymptomatic hyperuricaemia (SU levels ≥420 μmol/L), there was no significant difference in the mean estimated glomerular filtration rate (eGFR) slope between febuxostat and placebo groups.[42, level I] Another RCT showed similar results between febuxostat and non-febuxostat (allopurinol or placebo) groups in elderly patients (≥65 years old) with asymptomatic hyperuricaemia (SU levels ≥420 μmol/L) and ≥1 risks of CV/cerebral/renal disease.[45, level I] The quality of both RCTs was moderate.

A non-randomised controlled trial comparing febuxostat and allopurinol in patients with CKD stages 3-5 with asymptomatic hyperuricaemia (SU levels ≥420 μmol/L) showed a decrease in eGFR in allopurinol group among patients with CKD stage 3, 4, and 5 ($p<0.05$) compared with febuxostat. In the febuxostat group, there was an increase in eGFR in CKD stage 3 only and decrease in eGFR in CKD stage 4 and 5. The differences between the febuxostat and allopurinol groups were significant in CKD stage 3 and 4 but nonsignificant in CKD stage 5.[46, level II-1]

In terms of safety, the above meta-analysis showed no significant difference in the incidence of skin rash between allopurinol and placebo groups.[43, level I] There was also no significant difference in serious adverse events (SAEs) between allopurinol and placebo groups in the RCT involving type 1 diabetic patients with kidney disease. However, there were numerically more fatal SAEs in the allopurinol arm.[44, level I] There was no significant difference in AEs between febuxostat and placebo[42, level I] or febuxostat and allopurinol.[46, level II-1]

c. Urate-lowering therapy for cardioprotective effect in asymptomatic hyperuricaemia

Epidemiological studies have shown strong associations between SU levels with CV disease. However, it remains unclear whether hyperuricaemia directly or indirectly increases the risk of CV disease, as these associations are confounded by other risk factors e.g. obesity and hypertension.

An RCT compared febuxostat and non-febuxostat (allopurinol or placebo) treatments in elderly patients (≥65 years old) with asymptomatic hyperuricaemia (SU levels ≥420 μmol/L) and ≥1 risks of CV/cerebral/renal disease. It showed that the primary composite event rate (CV, cerebral or renal events and all deaths) was lower in the febuxostat group at 36 months (HR=0.750, 95% CI 0.592 to 0.950).[45, level I]

In a Cochrane systematic review of three RCTs on ULTs in patients with hypertension or prehypertension plus hyperuricaemia, there was insufficient evidence on the effect of ULTs in reducing blood pressure (BP). Analysis showed no significant difference in 24-hour ambulatory systolic or diastolic BP between those who received ULT and placebo. However, subgroup analysis demonstrated that ULTs reduced clinic-measured systolic BP (MD= -8.43 mmHg, 95% CI -15.24 to -1.62) but not diastolic BP among adolescents.[47, level I]

A recent meta-analysis comparing ULTs with placebo in adult heart failure patients showed that ULTs did not improve left ventricular ejection fraction, 6-minute walk test, brain natriuretic peptide/N-terminal-pro-brain natriuretic peptide (BNP/NT-pro-BNP), all-cause mortality and CV death among the patients. The quality of the primary papers included was high to moderate.[48, level I]

In terms of safety, no AEs were reported. The occurrence of malignant tumours was similar in the febuxostat and non-febuxostat groups.[45, level I] There were also inconclusive results regarding the occurrence of AEs when comparing between those who received ULTs and placebo.[47, level I]

- There is insufficient evidence from current studies to recommend ULT in asymptomatic hyperuricaemia to prevent gout, disease progression in CKD or CV events.

11. TREAT-TO-TARGET

Achieving SU target over time leads to suppression of gout flares as well as reduction of tophi size and number.

In a two-year RCT on T2T strategy aiming for SU <360 µmol/L in gout patients, community-based nurse-led care involving a T2T strategy was better in achieving SU target concentration compared with general practitioner-led usual care (RR=3.18, 95% CI 2.42 to 4.18). It also improved patient-centred outcomes:[49, level I]

- ≥2 flares (RR=0.33, 95% CI 0.19 to 0.57)
- ≥4 flares (RR=0.09, 95% CI 0.02 to 0.36)
- presence of tophi (RR=0.21, 95% CI 0.08 to 0.52)

Post hoc analysis comparing patients with and without renal impairment in the nurse-led group showed no difference in proportion of ULT use, achievement in SU of <360 µmol/L or <300 µmol/L, and AEs.

In another RCT on gout patients, comparing allopurinol dose escalation using T2T strategy aiming for SU <6 mg/dL (360 µmol/L) and control [Creatinine clearance (CrCl)-based allopurinol dose], the final SU reduction was greater in the dose escalation group at 12 months (MD=1.2 mg/dL (72 µmol/L), 95% CI 0.67 to 1.5). However, there were no significant differences in proportion of patients having any gout flare and change in tophus size in both groups. There were also no significant differences in renal function changes and SAEs.[50, level I]

A large cohort study on Korean adults showed that the lowest and highest SU categories were associated with an increased all-cause mortality when compared with the reference category [6.5 -7.4 mg/dL (390 - 444 µmol/L) in men; 3.5 - 4.4 mg/dL (210 - 264 µmol/L) in women]:[51, level II-2]

- Lowest SU category vs reference category
  - <3.5 mg/dL (210 µmol/L) for men with HR of 1.58 (95% CI 1.18 to 2.10)
  - <2.5 mg/dL (150 µmol/L) for women with HR of 1.80 (95% CI 1.10 to 2.93)
- Highest SU category vs reference category
  - ≥9.5 mg/dL (570 µmol/L) for men with HR of 2.39 (95% CI 1.57 to 3.66)
  - ≥8.5 mg/dL (510 µmol/L) for women with HR of 3.77 (95% CI 1.17 to 12.17)

ACR, EULAR and BSR recommend to achieve and maintain an SU target of <6 mg/dL (360 µmol/L) for all gout patients receiving ULT.[3; 52 - 53] The CPG DG recommends that the same SU target of <6 mg/dL (360 µmol/L) is used for all Malaysian gout patients receiving ULT as well.

- A lower SU target of <5 mg/dL (300 μmol/L) for faster dissolution of crystals is recommended in severe gout (tophi, chronic arthropathy, frequent flares). However, some studies have suggested that urate might be protective against various neurodegenerative diseases, therefore prolonged SU <3 mg/dL (180 μmol/L) is not recommended.[53]

Recommendation 4

- Treat-to-target strategy aiming for serum urate of <360 μmol/L should be applied in the treatment of all gout patients.

12. TREATMENT

Treatment of gout flare serves to provide rapid and effective pain relief enabling a return to previous activities. Long-term management is aimed at achieving a sustained reduction in SU level and consequent reduction in gout flares. There are various treatment modalities which include non-pharmacological, pharmacological and surgical approaches.

12.1 Non-pharmacological Treatment

The following are non-pharmacological treatments that have been proven to reduce recurrent gout flares or improve other outcomes.

a. Health education

Patient education is important to achieve SU target and treatment adherence among gout patients.

A systematic review of five RCTs and three cohort studies looked into the effectiveness of educational/behavioural interventions in gout. The interventions were delivered either by primary care providers, pharmacists or nurses. Quantitative analysis of four RCTs showed that educational/behavioural interventions were more effective than usual care in achieving SU <6 mg/dL (360 μmol/L) among gout patients (OR=4.86, 95% CI 1.48 to 15.97). Qualitative analysis of all five RCTs showed that there were also improvements in other outcomes e.g. adherence to allopurinol, a decrease of at least 2 mg/dL (120 μmol/L) in SU, achievement of SU <5 mg/dL (300 μmol/L), reduction in the number of tophi at two years etc. These findings were also supported by the three cohort studies included in the review. GRADE assessment of the evidence showed a rating of low to moderate quality.[54, level I]

Health education is strongly recommended as part of gout management. It consists of education on:[3, 52 - 53]

- pathophysiology of gout
- recognition of gout flare
- existence of effective treatments
- prompt treatment of gout flare and its principles
- compliance to ULT including T2T strategy
- continuance of ULT during flare
- healthy lifestyle
- associated comorbidities

b. Lifestyle modifications

- **Weight management**

A systematic review of low to moderate quality studies showed that compared with not losing weight after medium/long-term follow-up, weight loss (3 - 34 kg) in overweight/obese gout patients was associated with:[55, level II-2]

- decreased SU (range from -168 to 30 μmol/L)
- achievement of SU target (<360 μmol/L) in 0% to 60% of patients
- fewer gout flares (75% of the included studies showed beneficial effects on gout flares)

- **Dietary purine**

In a case-crossover study on purine-rich food intake in patients with gout, the following findings were noted:[56, level II-2]

- total purine intake in the highest quintile (median=3.48 g) over a 2-day period increased the risk of recurrent gout flares by almost five times compared with the lowest quintile (median=0.85 g) (OR=4.76, 95% CI 3.37 to 6.74); with a significant trend of higher risk in increasing quintile
- animal purine sources - the highest quintile of total purine intake increased risk of recurrent flares compared with the lowest quintile (OR=2.41, 95% CI 1.72 to 3.36)
- plant purine sources - the difference in recurrent gout flares was not statistically significant between the highest and lowest total purine intake
- impact from animal purine sources was substantially greater than that from plant purine sources

- **Alcohol consumption**

A case-crossover study confirmed that episodic alcohol consumption, regardless of type of alcoholic beverage (wine, beer or liquor), was associated with an increased risk of recurrent gout flares.[57, level II-2]

- Risk of recurrent gout flares increased significantly with >2 servings of alcoholic beverages compared with no alcohol consumption in the prior 24 hours (OR=1.51, 95% CI 1.09 to 2.09); a significant dose-response relationship between amount of alcohol consumption and risk of recurrent gout flares was noted (p<0.001 for trend).

*One typical drink contains approximately 15 grammes of alcohol.

- **Omega-3 polyunsaturated fatty acids**

Omega-3 PUFAs (n-3 PUFAs) have been shown to have anti-inflammatory effects through rapid and selective inhibition of the NLRP3 inflammasome.[58 - 61] Examples of dietary n-3 PUFA-rich fish (fatty fish) are anchovies, mackerel, salmon, sardines, trout and herring while n-3 PUFA-rich supplements are fish oil and cod liver oil. A case-crossover study on gout patients showed that:[22, level II-2]

- dietary n-3 PUFA-rich fish consumption of ≥2 servings in the prior 48 hours was associated with lower risk of recurrent gout flares compared with no fatty fish consumption (OR=0.74, 95% CI 0.54 to 0.99)
- n-3 PUFA-rich supplements were not associated with reduction in recurrent gout flares

- **Cherry**

Cherry products contain high levels of anthocyanins[62 - 64] that possess anti-inflammatory and antioxidant properties.[63; 65 - 66] A case-crossover study on gout showed that compared with no intake in the preceding 48 hours, the risk of gout flares was decreased by:[67, level II-2]

- 35% with cherries only intake (OR=0.65, 95% CI 0.50 to 0.85)
- 45% with cherry extract only intake (OR=0.55, 95% CI 0.30 to 0.98)
- 37% with cherries and cherry extract intake (OR=0.63, 95% CI 0.49 to 0.82)

When cherry intake was combined with allopurinol, risk of gout flares was 75% lower than periods without either exposure (OR=0.25, 95% CI 0.15 to 0.42).
However, more evidence is needed on the effect of cherry on gout.

- **High-fructose corn syrup**

ACR recommends to limit high-fructose corn syrup intake for patients with gout, regardless of disease activity.[52]

- **Others**

Gout patients are advised to stay well-hydrated, exercise and cease smoking.[68]

c. Concomitant medications

Medications that increase risk of gout should be discontinued or replaced with alternatives if possible. The decision to discontinue a medication should be made based on consideration of its benefits weighed against risks in patients. Refer to **Table 1** on **Risk factors for gout**.

- **Low-dose aspirin**

A case-crossover study on gout showed that compared with no aspirin use, the risk of gout flares increased by 81% (OR=1.81, 95% CI 1.30 to 2.51) for ≤325 mg/day of aspirin use on two consecutive days. The risk of gout flare was higher with lower doses (OR=1.91 for ≤100 mg, 95% CI 1.32 to 2.85). Concomitant use of allopurinol nullified the detrimental effect of aspirin on gout flares (OR=0.89, 95% CI 0.55 to 1.44).[69, level II-2]

The CPG DG recommends that aspirin if taken for appropriate indications should not be discontinued in gout patients as there are limited alternatives. Patients' SU should be monitored and ULT dose adjusted to achieve target as this may help to avoid flares.

Recommendation 5
- To improve outcomes in the management of gout:
  - health education and behavioural intervention should be offered
  - the following lifestyle modifications should be encouraged:
    - reduce weight in those who are obese/overweight
    - limit intake of purine-rich food especially of animal origin except omega-3 polyunsaturated fatty acid-rich fish
    - limit intake of all types of alcohol (beer, wine and liquor)
    - limit intake of high-fructose corn syrup

d. Topical ice

A gout flare can cause extreme pain, which affects a patient's ability to focus on work or perform other daily activities.

A Cochrane systematic review of one small RCT with high risk of bias studied the effectiveness of ice packs in reducing gout pain among patients treated with colchicine and prednisolone. Ice packs reduced pain compared with control (MD= -3.33 cm on VAS, 95% CI -5.84 to -0.82). Although ice packs reduced swelling, difference between the groups was not significant.[70, level I]

During gout flare, the affected joints should be rested, elevated and exposed in a cool environment.[3] Ice packs can be used as adjuvant treatment.[3; 52]

- Ice packs should always be applied over a cloth and not directly onto the skin of the affected joint (refer to **Appendix 4**).

Recommendation 6
- Ice packs may be used during gout flare.

12.2 Pharmacological Treatment

a. Urate-lowering therapy

The mainstay of gout treatment is ULT. Several types of ULT are now available e.g. xanthine oxidase inhibitors (allopurinol and febuxostat), uricosuric agents (benzbromarone and probenecid) and recombinant uricases (pegloticase).

- **Indications for urate-lowering therapy**

- Established indications to initiate ULT for gout patients are:[3; 52 - 53]
  - recurrent gout flares (≥2 flares in 12 months) **OR**
  - presence of ≥1 tophi **OR**
  - presence of radiographic damage attributable to gout

In addition, ACR conditionally recommends ULT initiation for gout patients with their first gout flare based on the following indications:[52]

- moderate to severe CKD (stage ≥3) **OR**
- SU concentration >9 mg/dL (540 μmol/L) **OR**
- urolithiasis

ACR also conditionally recommends initiating ULT for gout patients who previously experienced >1 flare but have infrequent flares (<2/year).[52]

For dosing of medications used in gout treatment, refer to **Appendix 5** on **Pharmacological Treatment for Gout**.

- **Allopurinol**

A Cochrane systematic review studied the effectiveness of allopurinol and other modalities of gout treatment in achieving SU target and showed:[71, level I]

- more patients on allopurinol achieved SU target compared with placebo in two RCTs [RR of 49.11 (95% CI 3.15 to 765.58) and 49.25 (95% CI 6.95 to 349.02) respectively]
- no difference in proportion of patients who achieved the SU target between allopurinol and benzbromarone
- allopurinol 100 - 300 mg daily had fewer patients achieving SU target compared with febuxostat 80 mg (RR=0.55, 95% CI 0.48 to 0.63), 120 mg (RR=0.48, 95% CI 0.42 to 0.54) and 240 mg (RR=0.42, 95% CI 0.36 to 0.49) daily but showed no difference with febuxostat 40 mg daily

The quality of the included papers was low to moderate. It has to be noted that in the RCTs comparing efficacy of allopurinol and febuxostat in lowering SU, allopurinol dose was not optimised and the highest dose used was only 300 mg daily.

Traditionally, it was recommended that ULT is initiated after resolution of gout flare. A meta-analysis of three RCTs showed that initiation of allopurinol during a flare did not significantly increase pain severity compared with placebo. The duration of flare also did not significantly differ between the two groups. The primary papers included were of moderate to high quality.[72, level I] ACR conditionally recommends that ULT can be initiated during gout flare.[52] Although sample sizes of the included studies in the above meta-analysis were small, the CPG DG opines that ULT can be initiated during a flare as long as the flare is being appropriately managed.

Allopurinol has been associated with several AEs. Most are mild GI events. The most serious AE is severe cutaneous adverse reaction (SCAR) which can be fatal.[73, level II-2] Reported risk factors for Allopurinol Hypersensitivity Syndrome (AHS) include the starting dose of allopurinol, presence of renal impairment and genetic allele HLA-B*58:01.[73, level II-2; 74, level I]

A case-control study demonstrated a relationship between allopurinol starting dose and AHS. The median time from starting allopurinol to developing AHS was 30 days (range 1 - 1080 days) and 90% of AHS cases occurred within the first 180 days. There was a strong dose-response relationship between the starting dose of allopurinol (adjusted for eGFR) and risk of AHS (p=0.001). AHS cases:

- had higher starting dose of allopurinol (p<0.001)
- were more likely to have a higher allopurinol starting dose than CrCl-based dose (OR=16.7, 95% CI 5.7 to 47.6)

Based on an ROC analysis, an allopurinol starting dose of 1.5 mg/unit eGFR minimised risk of AHS.[73, level II-2] Therefore, start allopurinol at low dose, 50 or 100 mg (refer to **Appendix 5**) and increase dose slowly every four weeks ("start low, go slow").

Two systematic reviews on gout showed no significant difference in any AEs between allopurinol (up to 300 mg daily) and:

- placebo[71, level I]
- febuxostat (40 and 240 mg daily)[71, level I; 75, level I]

However, allopurinol had more AEs compared with febuxostat 80 mg (RR=1.06, 95% CI 1.01 to 1.12) and 120 mg (RR=1.12, 95% CI 1.05 to 1.20).[71, level I]

In the Cochrane systematic review, there was also no significant difference in AEs between allopurinol (100 - 600 mg daily), benzbromarone (up to 200 mg daily) and probenecid (2 g daily).[71, level I] Quality of the primary papers in both reviews ranged from low to high.[71, level I; 75, level I]

HLA-B*58:01 is an allele carried mostly by the Han Chinese, Korean and Thai people. It is strongly associated with SCAR (OR=44.0, 95% CI 21.5 to 90.3). The gene dosage effect of HLA-B*58:01 influences the development of allopurinol-induced cutaneous adverse drug reactions:[74, level I]

- heterozygous (OR=15.25, 95% CI 8.40 to 27.70)
- homozygous (OR=72.45, 95% CI 14.70 to 356.70)

Both HLA-B*58:01 and renal impairment increase the risk of allopurinol-induced cutaneous adverse drug reactions. The odds of SCAR in:[74, level I]

- heterozygous allele and normal renal function (OR=15.25, 95% CI 8.40 to 27.70)
- homozygous allele and severe renal impairment (OR=1269.45, 95% CI 192.30 to 15,260.10)

On another note, a study showed that HLA-B*58:01 genetic testing before allopurinol initiation was unlikely to be a cost-effective intervention in Malaysia.[76, level I] Therefore, the CPG DG opines that routine screening of HLA-B*58:01 prior to commencement of allopurinol is not recommended.

- **Febuxostat**

Febuxostat is a potent non-purine selective XOI. A Cochrane systematic review of four RCTs with the following comparisons showed:[77, level I]

- febuxostat vs placebo
  - febuxostat was more likely to achieve SU levels <6.0 mg/dL (360 µmol/L)
    - 40 mg at 4 weeks (RR=40.1, 95% CI 2.5 to 639.1)
    - 80 mg at 4 - 28 weeks (RR=68.9, 95% CI 13.8 to 343.9)
    - 120 mg at 4 - 28 weeks (RR=80.7, 95% CI 16.0 to 405.5)
    - 240 mg at 28 weeks (RR=93.04, 95% CI 13.23 to 654.45)
- febuxostat vs allopurinol (200 - 300 mg)
  - febuxostat 40 mg showed no significant difference in achieving SU <6.0 mg/dL (360 µmol/L)
  - febuxostat 80 mg, 120 mg and 240 mg were more likely to achieve SU levels <6.0 mg/dL (360 µmol/L) at:
    - 24 - 52 weeks (RR=1.80, 95% CI 1.55 to 2.09)
    - 28 - 52 weeks (RR=2.16, 95% CI 1.91 to 2.45)
    - 28 weeks (RR=2.30, 95% CI 1.94 to 2.73)

In terms of safety, there was no significant difference in any AE (liver function test abnormalities, skin reactions, CV events, hypertension and diarrhoea) between febuxostat of any dose and placebo. In another comparison, febuxostat had lower total AEs than allopurinol:

- 80 mg with RR of 0.93 (95% CI 0.87 to 0.99)
- 120 mg with RR of 0.90 (95% CI 0.84 to 0.96)

There was no significant difference in any AEs between febuxostat 40 mg or 240 mg and allopurinol 200 - 300 mg. Risk of bias of the included primary papers ranged from low to high.

Two post-marketing studies looked into the CV safety of febuxostat. To fulfill the requirements of the United States (US) Food and Drug Administration (FDA), a large RCT [Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES)] on gout patients with pre-existing CV disease was conducted. Febuxostat was found to be noninferior to allopurinol in the overall rates of major CV events (p=0.002 for noninferiority). However, HR for deaths from any cause or CV events was 1.22 (95% CI 1.01 to 1.47) and 1.34 (95% CI 1.03 to 1.73) respectively.[78, level I] Nonetheless, this study has its limitations which include a high dropout rate in both the febuxostat and allopurinol groups.

In a large open-label RCT [The Febuxostat versus Allopurinol Streamlined Trial (FAST)] on gout patients with at least one CV risk factor commissioned by the European Medicines Agency, febuxostat was noninferior to allopurinol with regard to the occurrence of major CV outcomes (primary outcome of hospitalisation for nonfatal myocardial infarction or biomarker-positive acute coronary syndrome, nonfatal stroke, or death due to a CV event) with HR of 0.85 (95% CI 0.70 to

1.03). In this trial, febuxostat was not associated with increased risk of death or serious AEs.[79, level I]

Following the CARES trial, febuxostat has since carried a black box warning issued by FDA regarding the increased rate of CV death in gout patients with established CV disease.

Approximately one-quarter of patients with gout have CKD stage 3 and above.[30, level II-2] Thus, there is a need for effective and safe ULT for them. In an RCT of patients with renal function ranging from normal to severely impaired (eGFR 15 - 29 ml/min), febuxostat (40 mg and 80 mg, either extended release or immediate release) was more effective than placebo in achieving an SU level of <5.0 mg/dL (300 μmol/L) and <6.0 mg/dL (360 μmol/L) at month three ($p<0.001$ for all comparisons vs placebo). There were similar proportions of patients who experienced ≥1 gout flares across the treatment groups. The rates of treatment-emergent AEs (TEAEs) were low and evenly distributed between treatment arms. However, the overall incidence of TEAEs was higher in the severe renal impairment subgroup compared with the other subgroups.[80, level I]

- **Uricosuric agents**

In a Cochrane systematic review on uricosuric agents in chronic gout, the following results were demonstrated:[81, level I]

  - comparison between benzbromarone and allopurinol showed no significant difference in SU target achievement and AEs
  - benzbromarone was more effective than probenecid in SU target achievement after two months (RR=1.43, 95% CI 1.02 to 2.00: NNTB=5) but not in frequency of gout flares
  - benzbromarone also caused less AEs compared with probenecid (risk difference= -0.27, 95% CI -0.42 to -0.11)

- **Combination therapy**

Uricosuric agents can be used in combination with XOI in gout patients who do not achieve SU target with optimal doses of XOI monotherapy.[3; 53; 68]

- **Pegloticase**

Two RCTs on patients with severe gout, allopurinol intolerance or refractoriness, and SU concentration ≥8.0 mg/dL (480 μmol/L) showed significantly higher proportion of responders [plasma UA <6.0 mg/dL (360 μmol/L) for ≥80% of the time at three and six months] in patients on pegloticase compared with placebo. However, there were more SAEs in the pegloticase group. Gout flare and infusion-related reactions were the two commonest AEs.[82, level I] ACR recommends pegloticase in chronic gouty arthritis patients for whom treatment with XOI, uricosurics and other interventions have failed to achieve SU target and who continue to have frequent gout flares (≥2 flares/year)

or have non-resolving subcutaneous tophi.[52] However, its use is limited because of its cost.

- Health care professionals should be aware of the potential severe AEs of allopurinol especially SCAR and its risk factors:
  - starting dose of allopurinol
  - presence of renal impairment
  - presence of genetic allele HLA-B*58:01
- Initiation dose of allopurinol should be based on eGFR. Refer to **Appendix 5**.
- Routine screening of HLA-B*58:01 prior to commencement of allopurinol is not recommended locally.
- Febuxostat can be used in patients with renal impairment (eGFR 15 - 89 ml/min). However, uricosuric agents are contraindicated in patients with urolithiasis[3] and not recommended in severe renal impairment.

Recommendation 7
- Patients with gout should be treated with urate-lowering therapy when indicated.
  - Allopurinol is the first-line therapy. It should be started at low dose and increased gradually.
  - When allopurinol is contraindicated or not tolerated, febuxostat or uricosuric agents may be considered.

b. Gout flare

Gout flare is an extremely painful condition and can be very disabling. It needs to be treated promptly and adequately. The mainstay of treatment is pain relief.

- **Colchicine**

In a Cochrane systematic review of two RCTs, low dose (1.2 mg stat and 0.6 mg one hour later; total 1.8 mg over one hour) and high dose (1.2 mg stat, then 0.6 mg hourly for six hours; total 4.8 mg over six hours) colchicine were more effective than placebo in achieving ≥50% decrease in pain from baseline:[83, level I]

- low dose colchicine vs placebo at:
  - 24 hours (RR=2.74, 95% CI 1.05 to 7.13)
  - 32 to 36 hours (RR=2.43, 95% CI 1.05 to 5.64; NNTB=5, 95% CI 2 to 20)
- high dose colchicine vs placebo at:
  - 24 hours (RR=2.88, 95% CI 1.28 to 6.48)
  - 32 to 36 hours (RR=2.16, 95% CI 1.28 to 3.65; NNTB=4, 95% CI 3 to 12)

Both colchicine doses showed no significant difference for the same outcome up to 36 hours.

There was no significant difference in GI AEs e.g. diarrhoea, vomiting or nausea between low dose colchicine and placebo. However, high dose colchicine caused more GI AEs than:[83, level I]

- placebo (RR=3.81, 95% CI 2.28 to 6.38; NNTH=2, 95% CI 2 to 5)
- low dose (RR=3.00, 95% CI 1.98 to 4.54; NNTH=2, 95% CI 2 to 3)

The primary papers were of low quality. In view of fewer side effects, the CPG DG opines that low dose colchicine is the preferred choice.

- **Nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors**

A Cochrane systematic review compared the efficacy and safety of various nonsteroidal anti-inflammatory drugs (NSAIDs)/ cyclooxygenase-2 (COX-2) inhibitors. There were no significant differences in effectiveness based on different outcomes between indomethacin and COX-2 inhibitors. In terms of safety, indomethacin had more total AEs (RR=1.56, 95% CI 1.30 to 1.86) including GI AEs (RR=2.35, 95% CI 1.59 to 3.48). However, there was no significant difference in serious AEs. In one of the RCTs in the review, high dose celecoxib (800 mg stat, 400 mg 12 hours later, then 400 mg BD for seven days) showed no significant difference in patients' assessment of pain intensity compared with indomethacin 50 mg TDS. Celecoxib had significantly less AEs compared with indomethacin. Quality of the primary papers was low to moderate.[84, level I]

A meta-analysis comparing etoricoxib (120 mg OD) and NSAIDs [indomethacin (50 mg TDS)/diclofenac (75 mg OD)] showed etoricoxib had better pain relief based on VAS (MD= -0.46, 95% CI -0.51 to -0.41) but non-significantly when measured with the 0 - 4 point Likert scale. Etoricoxib also had fewer drug-related AEs (RR=0.64, 95% CI 0.50 to 0.81) with no significant difference in SAEs.[85, level I] The included primary papers were of moderate quality.

- **Corticosteroids**

In a Cochrane systematic review, one RCT showed no difference in resolution of pain using VAS between prednisolone (30 mg OD for 5 days) and intramuscular (IM) diclofenac (75 mg) plus indomethacin (50 mg TDS for two days, then 25 mg TDS for three days) at two weeks. However, there were significantly more AEs in the diclofenac plus indomethacin-treated patients. Quality of the RCT was moderate.[86, level I]

Two other systematic reviews showed no significant difference in pain scores and mean pain reduction[84, level I] between corticosteroids and NSAIDs. There was also no significant difference in total AEs. The primary papers in these two reviews were of low to moderate quality.[84, level I; 87, level I]

There is no direct evidence from randomised trials on the use of intra-articular corticosteroids in gout. Evidence extrapolated from studies on

osteoarthritis and rheumatoid arthritis suggests it may be a safe and effective option in gout flare.

- **Interleukin-1 inhibitor**

A systematic review comparing interleukin-1 (IL-1) inhibitors with corticosteroids showed canakinumab had better effectiveness than IM triamcinolone acetonide 40 mg at 72 hours in:[88, level I]

  - pain reduction (MD= -10.6, 95% CI -15.2 to -5.9)
  - complete absence of swelling (RR=1.39, 95% CI 1.11 to 1.74; NNTB=9)
  - Patient Global Assessment (PGA) (RR=1.37, 95% CI 1.16 to 1.61)

However, canakinumab had more frequent AEs:

  - at least 1 AE (RR=1.2, 95% CI 1.1 to 1.4; NNTH=10)
  - at least 1 SAE (RR=2.3, 95% CI 1.0 to 5.2)

Canakinumab is not readily accessible in Malaysia due to its cost.

In patients with gout flare where response to monotherapy is insufficient, combinations of treatment can be used[3] depending on the severity of flares.[53]

Recommendation 8

- Gout flare should be treated promptly and adequately.
- In gout flare, the following monotherapy may be used*:
  - colchicine
  - nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors
  - corticosteroids
- Combination of the above may be used in gout flare if response to monotherapy is insufficient.

*The choice of drug will be guided by patient's comorbidities. Refer to **Appendix 5** on **Pharmacological Treatment for Gout** with regard to dosage and mode of administration.

c. Flare prophylaxis

Initiation of ULT leads to dissolution of MSU deposits which causes dispersion of crystals resulting in increased gout flares. Therefore, administrating a concomitant anti-inflammatory agent is necessary in gout to reduce flares and encourage treatment adherence.

A systematic review on gout flare prophylaxis showed that the use of colchicine or canakinumab after starting ULT (allopurinol or probenecid) reduced both gout flares and their severity.[89, level I]

- Two RCTs with mixed risk of bias showed that colchicine given for at least three months significantly reduced gout flares compared with placebo. In one of the two RCTs, severity of the flares based on VAS was also significantly lower.

- In another RCT with low risk of bias, a single dose of canakinumab (50 mg - 300 mg) or 4 x 4 weekly doses (50 mg, 50 mg, 25 mg, 25 mg) provided significant prophylaxis against flares compared with daily colchicine 0.5 mg.

In the fourth RCT with high risk of bias, colchicine 1 mg/day given for 7 - 9 months and 10 - 12 months were more effective than that given for 3 - 6 months. However, there was no significant difference between the groups who received colchicine for a longer duration. In terms of AEs, there were no significant differences between the groups in the three out of four RCTs included in the review.[89, level I]

An alternative method to reduce gout flare is a stepwise dose increase of ULT. In an RCT, stepwise dose increase of febuxostat, and fixed-dose febuxostat with low dose colchicine prophylaxis given for three months, significantly reduced gout flares compared with fixed-dose febuxostat alone. However, there was no difference in gout flares between the stepwise dose increase of febuxostat and low dose colchicine prophylaxis groups. There were no differences in AEs identified between the three groups.[90, level I]

In a cross-sectional study on chronic gouty arthritis, colchicine (mean dose of 0.5 mg OD) or corticosteroids (prednisolone equivalent, mean dose of 7.5 mg OD) prophylaxis given for six months reduced the frequency and severity of gout flares during initiation of febuxostat. However, colchicine was superior to corticosteroids in flare prophylaxis. Both prophylactic agents were well tolerated.[91, level III]

CPG DG opines that stepwise dose increase of ULT and/or concomitant colchicine should be the preferred method for gout flare prophylaxis. Corticosteroid is less favoured as prolonged usage is usually associated with corticosteroid-related adverse events. Canakinumab is least preferred due to its cost.

Recommendation 9

- Prophylaxis for gout flares should be used for at least three to six months when initiating urate-lowering therapy.
  - The preferred choices are stepwise dose increase of urate-lowering therapy and/or concomitant colchicine.

d. Special groups

i. Gout in chronic kidney disease

- **Urate-lowering therapy**

T2T strategy should be applied in the treatment of all gout patients including those with CKD.[49 - 50, level I; 92, level I]

Allopurinol is effective and safe in gout patients with CKD.[49 - 50, level I; 92, level I] It is the preferred first-line ULT in gout patients with moderate to severe CKD (stage ≥3).[52] Initiation dose is lower than that used in patients with normal renal function.[73, level II-2] Dose escalation is more gradual.

Febuxostat is also effective and safe in gout patients with CKD (eGFR 15 - 89 ml/min).[80, level I] It is the second-line ULT in moderate to severe CKD.[52] The dose for febuxostat does not need to be adjusted in mild-to-moderate CKD (CrCl of 30 - 89 ml/min) but is limited to 40 mg OD in severe CKD (CrCl of 15 - 29 ml/min).[93 - 94, level III]

Uricosurics are contraindicated in gout patients with urolithiasis[3] and not recommended in severe renal impairment.

- **Gout flare**

Colchicine should be avoided in severe CKD as its safety in this group has not been established.[53] NSAIDs should also be avoided in CKD due to its potential nephrotoxic effect.[95] Corticosteroids may be used in gout flares with severe CKD.[3]

Topical ice therapy is safe during gout flare in patients with concomitant CKD.

- **Flare prophylaxis**

Stepwise dose escalation of ULT reduces incidence of gout flares including those with CKD.[49, level I]

Colchicine at a reduced dose is a recommended prophylaxis treatment in gout patients with CKD.[53] Long-term use of corticosteroid for flare prophylaxis is not advisable due to its adverse effects. Avoid NSAIDs in CKD due to its potential nephrotoxic effect.[95]

- The presence of CKD in gout patients requires a lower starting dose of allopurinol and slower escalation of the dose.
- The maximum dose of allopurinol in gout patients with CKD should be determined by its tolerability and not by renal function. The maximum approved dose of allopurinol is 900 mg daily.[96]

Recommendation 10

- Treat-to-target strategy should also be applied in the treatment of gout patients with concomitant chronic kidney disease.

ii. Gout in pregnancy and lactation

There is paucity of evidence in the treatment of gout in pregnancy and lactation. The discussion in this section is based on the recommendations

in the ACR guidelines. Some of the recommendations put forward are extrapolated from evidence not directly on gout.

Colchicine may be used in pregnancy and breastfeeding for the treatment of rheumatological conditions including gout. NSAIDs should be avoided in the third trimester while non-selective NSAIDs are preferred over COX-2 specific inhibitors in the first two trimesters of pregnancy. However, NSAIDs may be used in breastfeeding. Corticosteroids may be used with caution in pregnancy and breastfeeding. Non-fluorinated corticosteroids (prednisone, prednisolone) are preferred over fluorinated corticosteroids (dexamethasone, betamethasone) as the former do not cross the placenta at low to moderate doses unlike the latter.[110]

In addition, FDA recommends to avoid NSAIDs in pregnancy at 20 weeks or beyond as they can cause rare but serious kidney injury to the unborn baby.[97]

There is inadequate data on the use of allopurinol, febuxostat, probenecid and benzbromarone in pregnancy. Topical ice is safe for gout flare in pregnant patients.

- There is paucity of evidence in the treatment of gout in pregnancy.
  - Medications are used only when benefits clearly outweigh the risks.

13. DISCONTINUATION OF URATE-LOWERING THERAPY

A systematic review of five observational studies on discontinuation of ULT in adults with gout, showed that recurrence of arthritis was high ranging from 36.4 to 81.0%. The mean time to relapse varied from 15.8 to 56.0 months with earliest relapses occurring at four months.[98, level II-2]

One of the cohort studies included in the systematic review showed that higher SU levels during ULT treatment (HR=1.57, 95% CI 1.18 to 2.08) and at follow-up after ULT discontinuation (HR=2.29, 95% CI 1.91 to 2.74) were independently associated with gout recurrence.

- ULT should be continued long-term in gout patients to prevent recurrence of gout.

14. ADJUNCTIVE TREATMENT

There are multiple adjunctive treatments that have been used in gout to augment the effect of ULT. They are discussed below.

- **Vitamin C**

Vitamin C has been believed to have urate lowering effect. In a small RCT of eight weeks duration, modest dosage of vitamin C 500 mg/day was not clinically significant in its urate lowering effect compared with allopurinol in gout.[99, level I]

- **Fibrates**

In a meta-analysis of six RCTs on patients with type 2 diabetes mellitus and hyperlipidaemia with mostly normal urate level, fibrate reduced plasma urate concentration compared with placebo (WMD= -1.50 mg/dL (-90 μmol/L), 95% CI -2.38 to -0.63). Subgroup analysis showed that fenofibrate was effective but not bezafibrate.[100, level I] The included primary papers were of moderate quality.

In a cross-sectional study on gout, patients co-treated with XOIs and fenofibrate had lower SU compared with those on allopurinol or febuxostat alone (p=0.043). There were no significant differences in the levels of creatinine, blood urea nitrogen, and aminotransferases between patients treated with and without fenofibrate.[101, level III]

- **Statins**

A meta-analysis on patients with dyslipidaemia showed atorvastatin increased SU level compared with fenofibrate [MD=1.48 mg/dL (88.8 μmol/L), 95% CI 0.88 to 2.08].[102, level I] The primary papers were of low quality.

In a more recent meta-analysis in patients with hypercholesterolaemia and CHD, statins reduced plasma urate compared with control (WMD= -25.58 μmol/L, 95 % CI -50.25 to -0.91). Among all the statins, only atorvastatin and simvastatin showed significant effect.[103, level I] The included primary papers had low to moderate quality of evidence.

- **Urine alkalinisers**

Regarding urine alkalinisation among hyperuricaemic patients, a small RCT showed no significant difference in urinary urate excretion and SU level with either allopurinol alone or when combined with citrate preparation. However, for subjects with CrCl <90 ml/min, combination therapy significantly increased CrCl values from 71.0 to 85.8 ml/min. There was no significant difference in AEs between the groups.[104, level I]

As for the types of urine alkalinisation, an RCT on gout patients treated with benzbromarone, citrate mixture group had lower proportion of

patients with two gout flares than sodium bicarbonate group (p=0.0037). However, there were no significant differences in mean SU level and urine pH at week 12 between the groups. There was also no significant difference in AEs between them.[105, level I]

- More evidence is warranted before adjunctive therapy can be recommended in the treatment of gout.

15. MONITORING AND FOLLOW-UP

Monitoring is essential in the management of gout to ensure compliance with the T2T strategy for optimal patient outcomes. Evaluation of possible drug-related AEs is also vital during the follow-up of patients. Patients should be concomitantly screened for associated comorbidities.

15.1 Clinical outcomes

The following clinical parameters should be monitored:

- height, weight, BMI, BP
- gout flares
- number and size of tophi
- joint damage

15.2 Treat-to-target strategy

The following tests are to be done 4-weekly while titrating the ULT dose until the SU target is achieved. Thereafter, they can be performed 6-monthly.

- **Serum urate**

SU is the key parameter in monitoring disease control in accordance with the T2T strategy.[49 - 50, level I]

- **Renal function test/profile**

Renal function test/RP is monitored in parallel with SU measurement as it influences therapeutic decisions as mentioned in **Subchapter 12.2**.

15.3 Drug-related adverse events

As allopurinol is the most widely used ULT, it is paramount that health care professionals are aware of its rare but potentially life-threatening hypersensitivity reactions.

- Allopurinol-induced SCAR
  - Educate patients to be alert to symptoms and signs e.g. rash, pruritus or other allergic skin reactions, unexplained eye redness and oral or genital ulcers.
  - Emphasise the importance of prompt discontinuation of the drug at their first occurrence and to seek medical advice early.

Rare but serious hypersensitivity reactions to febuxostat have also been reported in post-marketing experience.[106, level III]

Refer to **Table 4** for investigations that are done periodically for drug monitoring.

Table 4. Summary of investigations for T2T strategy, drug monitoring and screening of comorbidities associated with gout during follow-up

Investigation	Allopurinol	Febuxostat	Probenecid	Benzbromarone	Colchicine
FBC	Every 4 weeks during dose titration and then every 6 months when dose is stable	Every 4 weeks during dose titration and then every 6 months when dose is stable	Every 4 weeks during dose titration and then every 6 months when dose is stable	Annually	Every 3 months
LFT				Every 4 weeks for first 6 months and then every 3 months	
SU and RP	Every 4 weeks until SU <360 µmol/L then every 6 months				
FBS, FSL, Haemoglobin A1c (HbA1c)	At least annually				
Urine FEME	During clinical review (urine protein to creatinine ratio or albumin to creatinine ratio if there is concurrent hypertension/diabetes mellitus)				
Plain radiography of affected joints, USG KUB	Repeat when indicated				
ECG Echocardiogram (ECHO)	When clinically indicated				

Source:

1. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017;76(1):29-42.
2. Colchicine [package insert]. Malaysia: Noripharma; 2017.
3. Febuxostat [package insert]. Phatheon France: Astellas Pharma Malaysia; 2019.
4. MIMS Online (Available at: https://www.mims.com/).

Recommendation 11

- Monitoring of patients with gout should include:*
  - clinical outcomes
  - drug-related adverse events; notably allopurinol-induced severe cutaneous adverse reaction
  - blood investigations for adverse effects of drugs
  - serum urate and comorbidity screening

*Refer to above text and table.

16. REFERRAL

Gout is the most common inflammatory arthritis globally[2, level III] with the majority of patients managed in primary and general medical healthcare facilities.[107, level III] The benefit of understanding the entire patient and associated comorbidities enables the family care providers to have a holistic approach in treating gout and other associated complicated diseases.[108, level III] As family physicians and general physicians treat most of gout cases, they are encouraged to refer the more challenging and complex cases to the relevant specialties or subspecialties. The criteria for referral are summarised below.[68]

16.1 Referral criteria for rheumatology care

- Diagnostic indication
  - Diagnosis is uncertain in cases with atypical clinical presentations including suspected gout in
    - women with onset before menopause
    - men with early onset at age <30 years without predisposing risk factors for gout
- Therapeutic indication
  - Refractory to conventional therapy despite drug adherence
    - Gout flare that fails to resolve despite treatment as recommended by the CPG
    - Recurrent flares although SU target of <360 µmol/L is achieved
    - Failure to achieve SU target of <360 µmol/L after a trial of at least three months of allopurinol at a maximally tolerated dose
    - Tophaceous gout with progressive joint damage, active symptoms or growing tophi despite medical treatment
  - Complicated gout with destructive joint changes
  - Hypersensitivity or intolerance to allopurinol
- Special group indication
  - Gout in pregnancy

Surgical management for tophi is generally considered as a last resort. Tophi tend to recur if the underlying hyperuricaemia is not treated with ULT. Decreasing SU to target reduces the size and number of tophi and facilitates their complete resolution.[49, level I] However, surgical intervention may be considered when there is uncontrolled infection, entrapment neuropathy or risk of permanent joint destruction.[109, level III]

16.2 Referral criteria for orthopaedic/surgical care

- Current or impending debilitating complications of tophaceous deposits
  - Uncontrolled infection including discharging sinus
  - Ulceration with risk of infection
  - Entrapment neuropathy e.g. carpal tunnel syndrome at the wrist
  - Major joint destruction
  - Joint instability

  - Impaired joint motion that affects activities of daily living, work or safety
  - Functional impairment e.g. the inability to wear shoes or clothing
- Cosmetic surgery e.g. ear lobe tophi
  - Should be elective and only after an adequate trial of medical therapy, as risk of complications may outweigh benefits
- Urolithiasis (should be assessed by a urologist)

Post-surgical complications are mostly minor and delayed wound healing is the most common.

Recommendation 12

- Referral of gout patients to a rheumatologist may be considered for the following:
  - diagnostic indications
    - unclear diagnosis with atypical clinical presentations including suspected gout in
      - women with onset before menopause
      - men with early onset at age <30 years without predisposing risk factors for gout
  - therapeutic indications
    - refractory to conventional therapy despite drug adherence
      - gout flare that fails to resolve despite treatment as recommended by the CPG
      - recurrent flares although SU target of <360 µmol/L is achieved
      - failure to achieve SU target of <360 µmol/L after a trial of at least three months of allopurinol at a maximally tolerated dose
      - tophaceous gout with progressive joint damage, active symptoms or growing tophi despite medical treatment
    - complicated gout with destructive joint changes
    - hypersensitivity or intolerance to allopurinol
  - special group indication
    - gout in pregnancy
- Surgical management of tophi may be considered when there is:
  - uncontrolled infection
  - entrapment neuropathy
  - risk of permanent joint damage
- Gout with urolithiasis should be assessed by a urologist.

17. IMPLEMENTING THE GUIDELINES

Management of gout should be guided by the latest evidence and availability of local resources to provide quality care to patients. Several factors may affect the implementation of recommendations in the CPG.

17.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:

- availability of CPG to health care providers (hard copies and soft copies/online)
- regular seminar/conference/course for health care providers on management of gout including those involving professional bodies (e.g. Malaysian Society of Rheumatology)
- public awareness activities during World Arthritis Day
- involvement of governmental/non-governmental organisations e.g. Malaysian Society of Rheumatology and Arthritis Foundation of Malaysia
- accessibility to relevant multidisciplinary teams

Limiting factors in the CPG implementation include:

- limited awareness and understanding/knowledge in management of gout among health care providers
- variation in clinical management and preferences
- insufficient resources in terms of budget, expertise, access to diagnostic tests and medications (gout placed at low priority by stakeholders)
- misconception about the disease and its management by the public
- no national registry on gout

17.2 Potential Resource Implications

T2T strategy is an important concept in gout management. However, many clinicians especially those in the primary care may not know and understand it. T2T strategy entails proper investigations and treatment of gout patients so that crippling chronic gouty arthritis, disabling comorbidities, poor quality of life and premature death can be minimised or even avoided.

In T2T strategy, more visits and frequent blood investigations are required to ensure SU level of <360 μmol/L is achieved. This can be done by a dedicated team in both primary and secondary care. It should include trained allied health care professionals. They can also provide regular health education (pathogenesis and natural course of disease, lifestyle modification, diet and exercise as well as the importance of

adherence to treatment) on gout to improve patient empowerment. Apart from that, appropriate initiation and optimisation of ULT usage should be addressed well. Allopurinol 100 mg tablet should be readily available in primary care and general medicine.

The issues discussed above require adequate human and financial resources. As gout is the commonest arthritis globally and increasing in its prevalence, T2T strategy should be emphasised in gout management throughout all levels of care.

17.3 Clinical Audit Indicators

The following are proposed as clinical audit indicators for quality management of gout:

- Percentage of incident gout patients indicated for ULT in whom ULT is actually started

$$= \frac{\text{Number of incident gout patients indicated for ULT in whom ULT is actually started in a year}}{\text{Number of incident gout patients indicated for ULT in a year}} \times 100\%$$

- Percentage of incident gout patients who achieve SU level <360 μmol/L

$$= \frac{\text{Number of incident gout patients who achieve SU level <360 μmol/L in a period}}{\text{Number of incident gout patients in the same period}} \times 100\%$$

Implementation strategies will be developed following the approval of the CPG by MoH which include launching of the CPG, Quick Reference and Training Module.

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Appendix 1

EXAMPLE OF SEARCH STRATEGY

Clinical Question: What are the safe and effective pharmacological treatments for acute flare of gout?

1. GOUT/
2. gout*.tw.
3. ARTHRITIS, GOUTY/
4. (gouty adj1 arthriti*).tw.
5. CRYSTAL ARTHROPATHIES/
6. 1 or 2 or 3 or 4 or 5
7. ACUTE DISEASE/
8. (acute adj1 disease*).tw.
9. ACUTE PAIN/
10. (acute adj1 pain*).tw.
11. SYMPTOM FLARE UP/
12. (acute adj2 symptom flare*).tw.
13. (symptom adj2 (flare up* or flare-up* or flareup*)).tw.
14. (symptom adj2 flaring up*).tw.
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. 6 and 15
17. ANTI-INFLAMMATORY AGENTS,NON-STEROIDAL/
18. (anti-inflammatory adj1 analgesics).tw.
19. ((anti-inflammatory or anti inflamatory) adj2 (non-steroidal agent* or nonsteroidal agent*)).tw.
20. nsaids.tw.
21. CYCLOOXYGENASE 2 INHIBITORS/
22. ((cox2 or cox-2 or cox 2) adj1 inhibitor*).tw.
23. coxibs.tw.
24. ((cyclooxygenase 2 or cyclooxygenase-2) adj1 inhibitor*).tw.
25. ANALGESICS, NON-NARCOTIC/
26. ((nonnarcotic or non narcotic or non-narcotic) adj1 analgesic*).tw.
27. (nonopioid or non opioid or non-opioid) adj1 analgesic*).tw.
28. COLCHICINE/
29. colchicine.tw.
30. ADRENAL CORTEX HORMONES/

31. (adrenal cortex adj1 hormone*).tw.
32. corticoids.tw.
33. corticosteroids.tw.
34. GLUCOCORTICOIDS/
35. ((glucocorticoid or glucorticoid) adj1 effect*).tw.
36. glucocorticoid*.tw.
37. ADRENOCORTICOTROPIC HORMONE/
38. acth.tw.
39. (adrenocorticotrop* adj1 hormone*).tw
40. adrenocorticotropin.tw.
41. corticotrop*.tw.
42. GOUT SUPPRESSANTS/
43. (antigout adj1 agent*).tw.
44. antihyperuricemic*.tw.
45. (gout adj1 suppressant*).tw.
46. Interleukin-1 inhibitor.tw.
47. ANTI-INFLAMMATORY AGENTS/
48. ((antiinflammator* or anti-inflammator* or anti inflammator*) adj1 agents).tw.
49. (antiinflammatory* or anti-inflammator* or anti inflammator*).tw.
50. Canakinumab.tw.
51. Rilonacept.tw.
52. INTERLEUKIN 1 RECEPTOR ANTAGONIST PROTEIN/
53. Anakinra.tw.
54. interleukin 1 receptor antagonist protein.tw.
55. kineret.tw.
56. 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55
57. 16 and 56
58. limit 57 to (english language and humans and yr=”2008 -Current”)

Appendix 2

CLINICAL QUESTIONS

1. What are the accurate diagnostic tools/tests for gout?
2. What are the safe and effective preventive strategies in gout?
3. What are the safe and effective pharmacological treatments for acute flare of gout?
4. What are the safe and effective treatments for flare prophylaxis in gout?
5. What are the indications for urate-lowering therapy in asymptomatic hyperuricaemia?
6. What are the indications for urate-lowering therapy in gout?
7. What are the safe and effective urate-lowering therapies in gout?
8. What are the safe and effective adjunctive therapies in gout?
9. What are the safe and effective non-pharmacological treatments in gout?
10. When to escalate/de-escalate or discontinue urate-lowering therapies in gout?
11. What are the associated comorbidities and risk factors for cardiovascular disease in gout?
12. What are the criteria for referring patients with gout to rheumatologists?
13. What are the effective monitoring parameters in gout?

Appendix 3

A. ALCOHOL SERVING SIZE

Types of Drink (Percentage of alcohol)	1 Serving
Regular beer (5%)	12 fl oz (355 ml)
Malt liquor (7%)	8 - 9 fl oz (237 - 266 ml)
Wine (12%)	5 fl oz (147 ml)
Distilled spirits (40%) ○ Gin, rum, tequila, vodka, whiskey, etc.	1.5 fl oz (44 ml)

Adapted: National Institute on Alcohol Abuse and Alcoholism (NIAAA): What is a standard drink? (Available at: https://www.niaaa.nih.gov/alcohols-effects-health/overview-alcohol-consumption/what-standard-drink Accessed 2 August 2021)

B. DIETARY APPROACHES TO STOP HYPERTENSION (DASH) DIET RECOMMENDATIONS

- Eat more vegetables, fruits and whole grains
- Include low-fat/fat-free dairy products, fish, poultry, beans, nuts and vegetable oils
- Limit intake of saturated fats
- Limit intake of sugar-sweetened beverages and sweets

(Based on 1600 - 2000 kcal/day)

Food Group	Daily Servings	Serving Size	Types of Food
Grains	6 - 8	1 slice bread ½ cup cooked rice, *kuetiau*, *bihun*, pasta 1/3 cup noodles 1 cup rice porridge 1/3 piece chapati 1/2 piece tosai 1 piece idli 3 tbsp oats	Wholegrain bread and pasta, brown rice, chapati/pita bread, cereals and oatmeal, tosai, idli
Vegetables	3 - 5	1 cup raw leafy vegetables (ulam) ½ cup cut-up raw or cooked vegetable ½ cup vegetable juice	Broccoli, carrots, green beans, green peas, kale, potatoes, spinach, squash, sweet potatoes, tomatoes, long beans

Food Group	Daily Servings	Serving Size	Types of Food
Fruits	4 - 5	1 medium fruit	orange, apple, custard apple (*nona*), starfruit, pear, peach, persimmon, sapodilla (*ciku*), kiwi
		1 small	banana
		6 whole	hog plum (*kedondong*)
		2 whole (small)	mangosteen, plum
		8 pieces	duku langsat, grapes, langsat, longan, small water apple (*jambu air*)
		5 whole	lychee, rambutan
		5 slices	pomelo
		1 slice	papaya, pineapple, watermelon, soursop
		½ fruit	small mango, guava
		4 pieces	cempedak, jackfruit (*nangka*)
		3 pieces	prunes, dried dates
		2 medium seeds	durian
		20g (2 tablespoon)	raisin
		½ cup	fruit juice, frozen or canned fruit
		¼ cup	dried fruit
Low-fat/Skimmed milk and dairy products	2 - 3	1 cup milk or yogurt 1 slice cheese	Skimmed or low-fat milk, yogurt or cheese
Lean meats, poultry, fish	≤6	1 oz cooked meats, poultry or fish 1 egg	Select only lean and trim away visible fats; broil, roast or poach - remove skin from poultry
Nuts, seeds and legumes	3 - 5/week	½ cup nuts 2 tbsp peanut butter 2 tbsp seeds ½ cup cooked legumes (beans, peas)	Almonds, hazelnuts, mixed nuts, peanuts, walnuts, sunflower seeds, peanut butter, kidney beans, lentils, split peas

Food Group	Daily Servings	Serving Size	Types of Food
Fats and oils	2 - 3	1 tsp vegetable oil 1 tbsp mayonnaise 1 tsp soft margarine 2 tbsp salad dressing	Soft margarine, vegetable oil (e.g. canola, corn, olive, or safflower), low-fat mayonnaise, light salad dressing
Sweets/added sugars	≤5/week	1 tbsp sugar 1 tbsp jam or kaya	Jelly, pudding, sugar, gula melaka, kuih

Adapted: 1. National Institutes of Health (NIH), National Heart, Lung and Blood Institute: Your Guide to Lowering your Blood Pressure with DASH. (Available at: https://www.nhlbi.nih.gov/files/docs/public/heart/new_dash.pdf)
2. Malaysian Medical Nutrition Therapy Guidelines for Type 2 Diabetes Mellitus, 2013

C. DIETARY RECOMMENDATIONS FOR GOUT

1. Fluid intake of at least two litres a day unless on fluid restriction.

2. Healthy, balanced diet as in DASH diet recommendations.

3. Specific food recommendations:

a. Restriction advised

i. Animal-based purine-rich foods
- Meat extract (e.g. Bovril), bouillon, broth, consommé, gravy
- Internal organs
  - Brain
  - Heart
  - Sweetbread
  - Kidney
- Seafood (e.g. shellfish, scallop, shrimp, lobster)
- Goose
- Red meat (e.g. beef, pork, mutton)

ii. Fructose/Sugar
- High-fructose corn syrup
- Sugar-sweetened beverages
- High intake of fruit juices
- Honey
- Sugars, syrups, sweets
- Desserts
- Processed tomato sauce and chilli sauce
- Fruit jam

iii. Alcoholic beverages (e.g. beer, wine, liquor)

b. No restriction required

i. n-3 PUFA-rich fish*
- Anchovies
- Mackerel (*ikan kembung, tenggiri, makarel*)
- Herring (*ikan parang*)
- Sardines (*ikan sardin, tamban*)
- Salmon
- Trout

ii. Plant-based purine-rich foods#
- soy-based food and non-soy legumes e.g. peas, beans, lentils
- spinach
- mushrooms
- cauliflower
- oats
- nuts and seeds$

*Benefits of n-3 PUFA-rich fish in reducing cardiovascular events outweigh the potential detrimental effect derived from its high purine content.
#Plant-based purine-rich foods are not associated with increased risk of gout.
$Nuts and seeds are not associated with increased risk of gout.

Adapted:

1. Lichtenstein AH, Appel LJ, Vadiveloo M, et al. 2021 Dietary Guidance to Improve Cardiovascular Health: A Scientific Statement From the American Heart Association. Circulation. 2021;144(23):e472-e487.
2. Ministry of Health, Malaysia. Malaysian Dietary Guidelines 2020. Putrajaya: MoH; 2020.
3. Zhang M, Zhang Y, Terkeltaub R, et al. Effect of Dietary and Supplemental Omega-3 Polyunsaturated Fatty Acids on Risk of Recurrent Gout Flares. Arthritis Rheumatol. 2019;71(9):1580-1586.
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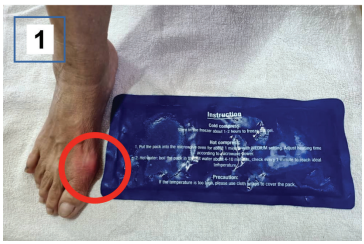
6. Zhang Y, Chen C, Choi H, et al. Purine-rich foods intake and recurrent gout attacks. Ann Rheum Dis. 2012;71(9):1448-1453.

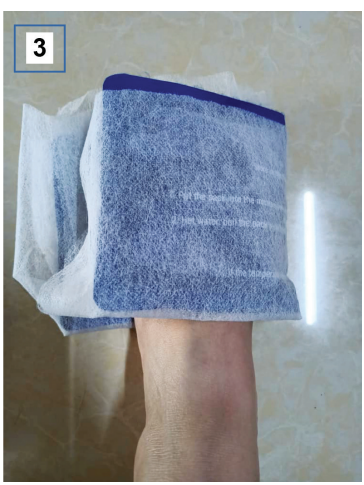
Appendix 4

APPLICATION OF ICE PACK



Use of ice pack for gout flare affecting first toe.

Wrap towel around ice pack.



Place wrapped ice pack around affected joint.

PHARMACOLOGICAL TREATMENT FOR GOUT
A. URATE-LOWERING THERAPY IN GOUT

<table>
<tr><th>Drug</th><th>Recommended dose</th><th>Possible AEs</th><th>Contraindication/ Caution</th><th>Common drug interaction#</th></tr>
<tr>
<td>Allopurinol</td>
<td>Initial: 100 mg/day, adjusted in increments of 100 mg every 2 - 4 weeks according to SU concentration until target is achieved
Maintenance: ≥300 mg/day are usually needed to reach the desired SU target
Maximum: 900 mg/day
Frequency: Once daily in a single dose or in 2 or 3 divided doses if >300 mg/day

Dosage modifications in renal impairment:
<table>
<tr><th>eGFR (ml/min /1.73m^2)</th><th>Initial dose</th><th>Dose increment</th></tr>
<tr><td>>60</td><td>100 mg daily</td><td>Increase by 100 mg every 4 weeks* if tolerated until SU target is reached or to a maximum of 900 mg daily</td></tr>
<tr><td>30 - 60</td><td>50 mg daily</td><td>Increase by 50 mg every 4 weeks if tolerated until SU target is reached or to a maximum of 900 mg daily**</td></tr>
<tr><td><30</td><td>50 mg every other day</td><td>Increase to 50 mg every day after 4 weeks, then increase by 50 mg every 4 weeks thereafter if tolerated until SU target is reached or to a maximum of 900 mg daily**</td></tr>
</table>
</td>
<td>Common:
• Dermatologic
Maculopapular rash, pruritus
• GI
Nausea, vomiting

Serious:
• Dermatologic
Hypersensitivity reactions ranging from mild maculopapular rash to severe cutaneous adverse reaction, including Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)
• Hepatic
Transaminitis, cholestasis
• Haematologic
Bone marrow suppression</td>
<td>Contraindication:
• Hypersensitivity to allopurinol

Caution:
• HLA-B*58:01 -positive patient</td>
<td>• Azathioprine/ mercaptopurine
Reduces metabolism of azathioprine and mercaptopurine; increases risk of bone marrow toxicity
• Warfarin
Prolongs half-life of warfarin
• Ciclosporin
May increase levels of ciclosporin
• Theophylline
May inhibit metabolism of theophylline</td>
</tr>
</table>

Drug	Recommended dose	Possible AEs	Contraindication/ Caution	Common drug interaction#
	*More rapid titration e.g. every 2 weeks is possible, although this needs to be balanced against the **increased risk of adverse effects** **Consider referral to or discussion with rheumatologist if SU targets are not achieved or increase in dose is not tolerated			
Probenecid	**Initial**: 250 mg BD for 1 week; may increase to 500 mg BD; if needed, may increase to a maximum of 1000 mg BD (increase dosage in 500 mg increment every 4 weeks) **Renal impairment of CrCl <30 ml/min**: Avoid use Maintain adequate fluid intake (2 - 3 L/day) if not on medically advised fluid restriction diet	**Common**: • **Dermatologic** Rash • **GI** Nausea, vomiting **Serious**: • **Dermatologic** SJS • **Haematologic** Aplastic anaemia, leukopenia, thrombocytopenia, neutropenia • **Hepatic**: Hepatic necrosis • **Immunologic**: Anaphylaxis, hypersensitivity reaction	**Contraindications:** • Hypersensitivity to probenecid • Urolithiasis • Blood dyscrasias	• **Aspirin** Aspirin decreases uricosuric action of probenecid • **Paracetamol/ naproxen/ lorazepam/ rifampicin/ acyclovir** Probenecid may increase their serum concentration • **Methotrexate** May potentiate methotrexate toxicity • **Sulphonylurea** Increases the hypoglycaemic effect of sulphonylurea

<table>
<tr><th>Drug</th><th>Recommended dose</th><th>Possible AEs</th><th>Contraindication/ Caution</th><th>Common drug interaction#</th></tr>
<tr><td></td><td></td><td></td><td></td><td>• Most beta-lactam antibiotics
Increases level of beta-lactam antibiotics</td></tr>
<tr><td>Febuxostat</td><td>Initial: 40 mg OD; if SU level is >6.0 mg/dL (360 µmol/L) after 2 - 4 weeks, 80 mg OD may be considered
Maintenance: 40 mg or 80 mg OD, dose may be increased to 120 mg OD if clinically indicated

Dosage modifications in renal impairment:<table><tr><th>CrCl (ml/min)</th><th>Dose</th></tr><tr><td>≥30</td><td>No adjustment</td></tr><tr><td>15-29</td><td>Maximum dose 40 mg OD</td></tr></table>Dosage modifications in hepatic impairment:<table><tr><th>CrCl (ml/min)</th><th>Dose</th></tr><tr><td>A or B</td><td>No adjustment</td></tr><tr><td>C</td><td>Use with caution</td></tr></table></td><td>Common:
• Dermatologic
Rash
• GI
Diarrhoea, nausea
• Hepatic
Liver function abnormalities

Serious:
• Dermatologic
DRESS, SJS, TEN

Black Box Warning
Cardiovascular:
• Gout patients with established CV disease treated with febuxostat had a higher rate of CV death compared with those treated with allopurinol in a CV outcomes study.
• Consider the risks and benefits when prescribing febuxostat or continuing treatment.</td><td>Contraindications:
• Hypersensitivity to febuxostat
• Concomitant use of azathioprine/ mercaptopurine due to increase in toxicity</td><td>• Azathioprine/ mercaptopurine
Increased plasma concentrations result in severe toxicity of azathioprine and mercaptopurine
• Methotrexate
May enhance hepatotoxic effect of methotrexate</td></tr>
</table>

Drug	Recommended dose	Possible AEs	Contraindication/ Caution	Common drug interaction#
		• Febuxostat should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol or whom treatment with allopurinol is not advisable.		• **Theophylline** May increase serum concentration of theophylline
Benzbromarone	Doses of 50 - 200 mg daily may be used Usual dose of benzbromarone is 50 - 100 mg/day **Renal impairment of eGFR <20 ml/min**: Avoid use Maintain adequate fluid intake (2 - 3 L/day) if not on medically advised fluid restriction diet	**Common**: • **GI** nausea, vomiting, diarrhoea • **Hepatic** May cause liver damage	**Contraindications:** • Urolithiasis	• **Warfarin** May increase effect of warfarin
Pegloticase	IV infusion 8 mg every 2 weeks	**Common**: • **Dermatologic** Urticaria • **GI** Constipation, nausea, vomiting **Serious**: • **Immunologic** Infusion-related reaction • **Haematologic** Glucose-6-phosphate dehydrogenase deficiency (G6PD) related anaemia • **CV** Congestive heart failure	**Contraindications:** • Hypersensitivity to pegloticase • G6PD deficiency	• Discontinue use of oral ULT agents prior to pegloticase therapy and do not initiate during the course of the therapy. These may delay interpretation of ineffective pegloticase treatment and increase risk of infusion reaction.

Drug	Recommended dose	Possible AEs	Contraindication/ Caution	Common drug interaction#
		Black Box Warnings **Anaphylaxis and infusion reactions**: Anaphylaxis may occur at any infusion rates. Patient should be premedicated with antihistamines and corticosteroids and closely monitored. **G6PD deficiency associated haemolysis and methaemoglobinaemia** Screen patients at risk of G6PD deficiency prior to initiation.		

#Dosage adjustment of the medications should be considered.

B. TREATMENT OF FLARE AND FLARE PROPHYLAXIS IN GOUT

<table>
<tr><th>Drug</th><th>Recommended dose</th><th>Possible AEs</th><th>Contraindication/ Caution</th><th>Common drug interaction#</th></tr>
<tr>
<td>Colchicine</td>
<td>Gout flare
Initial dose: 1 mg, then 0.5 mg after 1 hour. No further tablets should be taken for 12 hours.
After 12 hours, treatment can be resumed if necessary with a maximum dose of 0.5 mg every 8 hours until symptoms are relieved. The course of treatment should end when symptoms are relieved or when a total of 6 mg (12 tablets) has been taken. After completion of a course, another course should not be started for at least 3 days (72 hours).

Flare prophylaxis
0.5 mg OD or BD. Prophylactic therapy may be beneficial for at least the first 3 to 6 months of ULT therapy.

Treatment of gout flare during prophylaxis with colchicine
Do not exceed 1 mg at the first sign of flare, followed by 0.5 mg 1 hour later, wait for 12 hours and then resume prophylactic dose.

Initiate prophylactic dose at least 12 hours after treatment dose and continue until gout flare resolves.

Dosage modifications in renal impairment:
<table>
<tr><th>CrCl (ml/min)</th><th>Gout flare treatment*</th><th>Gout flare prophylaxis</th></tr>
<tr><td>>60 - 89</td><td>No dosage adjustment, monitor closely for AE</td><td>No dosage adjustment, monitor closely for AE</td></tr>
</table>
</td>
<td>Common:
• GI
Nausea, vomiting, diarrhoea

Serious:
• Haematologic
Myelosuppression
• Neuromuscular and skeletal
Neuromuscular disease, neuromyotoxicity</td>
<td>Contraindications:
• Concomitant use of drugs that are both P-glycoprotein and CYP3A4 inhibitors in patients with renal or hepatic impairment
• Concomitant use of P-glycoprotein or CYP3A4 inhibitors in patients with renal or hepatic impairment
• Patients with both renal and hepatic impairment
• Blood dyscrasia</td>
<td>• CYP3A4 inhibitor/P-glycoprotein inhibitor
Increased risk of toxicity
• Statin/fibrates/ digoxin/ ciclosporin
Increased risk of myopathy and rhabdomyolysis</td>
</tr>
</table>

<table>
<tr><th>Drug</th><th>Recommended dose</th><th>Possible AEs</th><th>Contraindication/ Caution</th><th>Common drug interaction#</th></tr>
<tr><td></td><td>
<table>
<tr><td>30 - 60</td><td>No dosage adjustment, monitor closely for AE</td><td>Limit dose to 0.5 mg daily</td></tr>
<tr><td><30, renal replacement therapy</td><td>Consider alternative therapy</td><td>Consider alternative therapy</td></tr>
</table>
*Use of colchicine to treat gout flares is not recommended in patients with renal impairment (CrCl <80 ml/min) already receiving prophylactic colchicine.

Dosage modifications in hepatic impairment:
<table>
<tr><th>Hepatic Impairment</th><th>Gout flare treatment**</th><th>Gout flare prophylaxis</th></tr>
<tr><td>Mild to moderate</td><td>No dosage adjustment, monitor closely for AE</td><td>No dosage adjustment, monitor closely for AE</td></tr>
<tr><td>Severe</td><td>Dosage adjustment not required but may be considered; treatment course should not be repeated more frequently than every 14 days</td><td>Consider dosage adjustment</td></tr>
</table>
**Use of colchicine to treat gout flares is not recommended in patients with hepatic impairment already receiving prophylactic colchicine.
</td><td></td><td></td><td></td></tr>
</table>

<table>
<tr><th>Drug</th><th>Recommended dose</th><th>Possible AEs</th><th>Contraindication/ Caution</th><th>Common drug interaction#</th></tr>
<tr><td></td><td>Dosage modifications in patients receiving or have recently (within 14 days) received a moderate or potent CYP3A4 inhibitor or an inhibitor of the P-glycoprotein transport system:
<table>
<tr><th>Recent or concomitant therapy</th><th>Gout flare treatment***</th><th>Gout flare prophylaxis</th></tr>
<tr><td>Potent CYP3A4 inhibitor e.g. clarithromycin, ketoconazole, itraconazole and certain protease inhibitors</td><td>0.5 mg at first sign of flare, followed by 0.25 mg one hour later</td><td>0.25 mg OD or every other day</td></tr>
<tr><td>Moderate CYP3A4 inhibitor e.g. diltiazem, erythromycin, fluconazole, verapamil</td><td>1 mg at first sign of flare</td><td>0.25 mg BD, 0.5 mg OD or 0.25 mg OD</td></tr>
<tr><td>P-glycoprotein inhibitor e.g. cyclosporin, ranolazine</td><td>0.5 mg at first sign of flare</td><td>0.25 mg OD or every other day</td></tr>
</table>
Use of colchicine to treat gout flares is not recommended in patients receiving prophylactic dose of colchicine and CYP3A4 inhibitors.
***Do not repeat courses of colchicine therapy until 3 days have elapsed.</td><td></td><td></td><td></td></tr>
</table>

Drug	Recommended dose	Possible AEs	Contraindication/ Caution	Common drug interaction#
NSAIDs/COX-2 inhibitors				
Ibuprofen	400 - 800 mg TDS (maximum: 3200 mg/day)	**Common**: • **GI** GI Intolerance • **CV** Elevated blood pressure, oedema • **Dermatological** Rash • **Hepatic** Abnormal LFT	**Contraindications**: • Hypersensitivity to NSAIDs • Perioperative pain in the setting of coronary artery bypass graft surgery • History of GI bleeding, perforation or ulceration related to NSAIDs therapy • Current GI bleeding, perforation or ulceration • Severe hepatic or renal impairment • Severe cardiac failure	• **Antiplatelets/ anticoagulants/ corticosteroids** Increased risk of GI bleeding • **Lithium** NSAIDs may increase serum concentration of lithium • **Methotrexate** Increased levels and risk of toxicity of methotrexate
Diclofenac	50 mg BD/TDS			
Naproxen	550 - 1100 mg in 2 divided doses (275 mg tablet) 750 mg initially, then 250 mg TDS (250 mg tablet)			
Meloxicam	Maximum 15 mg/day			
Celecoxib	400 mg stat followed by 200 mg BD subsequently			
Etoricoxib	120 mg/day			
Corticosteroids				
Prednisolone	**Flare treatment**: 30 to 40 mg/day once daily or in 2 divided doses for 5 days. If a longer duration is needed for more severe flare, a gradual taper over 7 to 10 days is an option.	**Common:** • **CV** Body fluid retention, hypertension • **Dermatologic** Acne	**Contraindications:** • Hypersensitivity to prednisolone • Concomitant administration	• **CYP3A4 inhibitors (e.g. ketoconazole)** May increase serum

Drug	Recommended dose	Possible AEs	Contraindication/ Caution	Common drug interaction[#]
	A slower taper (e.g. over 14 to 21 days) maybe required, particularly in patients with multiple recent flares.	• **GI** GI bleeding • **Endocrine metabolic** Decreased body growth, hyperglycaemia • **Musculoskeletal** Osteoporosis • **Neurologic** Headache	with live vaccines or live attenuated virus vaccines (with immunosuppressive doses of corticosteroids) **Caution**: • Active infections	concentration of prednisolone • **CYP3A4 inducers (e.g. phenobarbitone, rifampicin)** May decrease serum concentration of prednisolone • **NSAIDs** Increased risk of GI bleeding • **Anticoagulant** Increased risk of bleeding • **Loop diuretics** Enhances hypokalemic effect of loop diuretics
Triamcinolone	**Intra-articular:** Large joint: 40 mg as a single dose Medium joint: 30 mg as a single dose Small joint: 10 mg as a single dose **Intramuscular:** 40 to 80 mg as a single dose; May repeat at ≥48-hour intervals if there is no flare resolution	**Common**: • **Haematologic** Bruise • **Neuromuscular and skeletal** Joint swelling • **Respiratory** Cough, sinusitis	**Contraindications**: • Hypersensitivity to triamcinolone • Bleeding diastheses	• **Ciclosporin** Increase in both ciclosporin and corticosteroids activity when used concomitantly

[#]Dosage adjustment of the medications should be considered.

C. TREATMENT OF GOUT IN PREGNANCY AND LACTATION

Drug	Pregnancy	Lactation
Allopurinol	Category C	Limited human data; potential toxicity
Probenecid	Category B	Limited human data; probably compatible
Febuxostat	Category C	No human data; potential toxicity
Benzbromarone	No data	No data
Pegloticase	No data	No data
Colchicine	Category C	Limited human data; probably compatible
NSAIDs		
Ibuprofen	Restricted to first and second trimester	Compatible
Diclofenac		No human data; probably compatible
Naproxen		Limited human data; probably compatible
Meloxicam		No human data; probably compatible
COX-2 inhibitors		
Celecoxib	Should be avoided	Limited human data
Etoricoxib		No data
Corticosteroids		
Prednisolone	Category C	Compatible
Triamcinolone	Category C	No human data; probably compatible

FDA Pregnancy Categories

Category	Definitions
A	Generally acceptable Controlled studies in pregnant women show no evidence of fetal risk
B	May be acceptable Either animal studies show no risk but human studies not available or animal studies showed minor risks and human studies done and showed no risk
C	Use with caution if benefits outweigh risks Animal studies show risk and human studies not available or neither animal nor human studies done
D	Use in LIFE-THREATENING emergencies when no safer drug available Positive evidence of human fetal risk
X	Do not use in pregnancy (contraindicated) Risks involved outweigh potential benefits Safer alternatives exist
NA	Information not available

Boxed Warnings - US FDA
This type of warning is also commonly referred to as a "black box warning." It appears on a prescription drug's label and is designed to call attention to serious or life-threatening risks.

Adapted:
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2. Wolters Kluwer Clinical Drug Information, Inc. UpToDate® [Mobile application software]
3. Mims Gateway. (Available at: http://www.mimsgateway.com/malaysia/overview.aspx)
4. Micromedex® Solution. (Available at: https://www.micromedexsolutions.com/)
5. Managing gout in primary care, Controlling gout with long term urate-lowering treatment, The Best Practice Advocacy Centre New Zealand (bpacnz), 2021. (Available at: https://bpac.org.nz/2021/gout-part2.aspx)
6. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis. 2017;76(1):29-42
7. FDA adds Boxed Warning for increased risk of death with gout medicine Uloric (febuxostat), US Food & Drug Administration, 2019. (Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-increased-risk-death-gout-medicine-uloric-febuxostat)
8. Briggs GG and Freeman Roger K. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. 10th Edition. Philadelphia: Lippincott Williams & Wilkins; 2015;1-1579.
9. Hui M, Carr A, Cameron S, et al. The British Society for Rheumatology Guideline for the Management of Gout. Rheumatology (Oxford). 2017;56(7):e1-e20.

LIST OF ABBREVIATIONS

ACE inhibitors	Angiotensin-converting enzyme inhibitors
ACR	American College of Rheumatology
ADL	activities of daily living
AE(s)	adverse event(s)
AGREE (II)	Appraisal of Guidelines for Research and Evaluation II
AHS	Allopurinol Hypersensitivity Syndrome
AP	Anteroposterior
BCE	before common era
BMI	body mass index
BSR	British Society for Rheumatology
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disease
COX-2 inhibitors	cyclooxygenase-2 inhibitors
CPG(s)	clinical practice guidelines
CrCl	creatinine clearance
CT	computed tomography
CV(D)	cardiovascular (disease)
CXR	chest X-ray
DASH	Dietary Approaches to Stop Hypertension
DCS	double contour sign
DECT	dual-energy computed tomography
DG	development group
DRESS	drug reaction with eosinophilia and systemic symptoms
DVT	deep vein thrombosis
ECG	electrocardiogram
ECHO	echocardiogram
eGFR	estimated glomerular filtration rate
EULAR	European League Against Rheumatism
FBC	full blood count
FDA	Food and Drug Administration
fl oz	fluid ounce
GFR	glomerular filtration rate
GI	gastrointestinal
GRADE	Grading Recommendations, Assessment, Development and Evaluation
G-CAN	Gout, Hyperuricemia and Crystal-Associated Disease Network
HbA1c	haemoglobin A1c
HR	hazard ratio
IL-1	interleukin-1
IM	intramuscular
kcal/day	kilocalorie per day
kg/m^2	kilogramme per meter square
LFT	liver function test
MaHTAS	Malaysian Health Technology Assessment Section
MD	mean difference
mg	milligramme
mg/day	milligramme per day
mg/dL	milligramme per decilitre

µmol/L	micromol per litre
ml/min	millilitre per minute
MoH	Ministry of Health
MSU	monosodium urate
MTP	metatarsophalangeal
NNT	number needed to treat
NNTB	number needed to benefit
NNTH	number needed to harm
NSAID(s)	nonsteroidal anti-inflammatory drug(s)
n-3 PUFA(s)	omega-3 polyunsaturated fatty acid(s)
OD	once a day
OR	odds ratio
PAR	population attributable risks
PE	pulmonary embolism
PGA	Patient Global Assessment
RC	review committee
RCT(s)	randomised controlled trial(s)
RP	renal profile
ROC	receiver operating characteristic
RR	risk ratio
SAE(s)	severe adverse event(s)
SCAR	severe cutaneous adverse reaction
SJS	Stevens-Johnson syndrome
SF	synovial fluid
STAT	immediately
SU	serum urate
tbsp	tablespoon
TDS	three times a day
TEAE(s)	treatment-emergent adverse event(s)
TEN	toxic epidermal necrolysis
TFT	thyroid function test
tsp	teaspoon
T2T	treat-to-target
ULT	urate-lowering therapy
Urine FEME	full and microscopic examination of urine
US(A)	United States (of America)
USG KUB	ultrasound of the kidneys, ureters and bladder
VAS	Visual Analogue Scale
VTE	venous thromboembolism
vs	versus
WMD	weighted mean difference
XOI	xanthine oxidase inhibitor

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