CLINICAL PRACTICE GUIDELINES

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MANAGEMENT OF GOUT (SECOND EDITION)

Ministry of Health Malaysia

Malaysian Society of Rheumatology

Academy of Medicine Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and 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 hyperuricaemia and/or gout:
  - a healthy lifestyle should be advocated, which includes
    - maintenance of a healthy body weight (body mass index <25 kg/m^2)
    - avoidance of alcohol
    - adherence to Dietary Approaches to Stop Hypertension (DASH) diet
  - diuretics should be avoided if possible, or replaced by an alternative drug when used as an antihypertensive agent

Diagnosis

- Synovial fluid aspiration of an affected joint should be performed to examine for the presence of monosodium urate crystals to confirm the diagnosis of gout.
  - If aspiration is not feasible, the diagnosis may be made based on clinical manifestations.

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.
  - Allopurinol is the first-line therapy.
  - When allopurinol is contraindicated or not tolerated, febuxostat or uricosuric agents can be considered.

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 tests, especially serum urate
- Screening for associated comorbidities should be done upon diagnosis and follow-up.

Referral

- Referral of gout patients to a rheumatologist may be considered for the following indications:
  - unclear diagnosis
  - ineffective conventional therapy
  - destructive joint changes
  - allopurinol hypersensitivity or intolerance
  - early onset (<30 years old) without risk factors
  - onset before menopause
  - pregnancy
  - chronic kidney disease stage 3 and above
- 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 an urologist/surgeon.

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 were 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 requirement 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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Primary, secondary and tertiary care

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REVIEW COMMITTEE

The draft guidelines were reviewed by a panel of experts. They were asked to comment primarily on the comprehensiveness and accuracy of the interpretation of evidence supporting the recommendations in the guidelines.

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The following external reviewers provided feedback on the draft:

ALGORITHM ON MANAGEMENT OF GOUT

Acute monoarthritis

Clinical features highly suggestive of gout
Monoarticular involvement of a foot (especially the first MTP) or ankle joint
Previous similar acute arthritis episodes
Rapid onset of severe pain and swelling (at its worst in <24 hours)
Erythema
Male gender
Associated cardiovascular diseases
Hyperuricaemia

CKD: chronic kidney disease
COX-2 inhibitors: cyclooxygenase-2 inhibitors
MTP: metatarsophalangeal
NSAIDs: nonsteroidal anti-inflammatory drugs
SU: serum urate
ULT: urate-lowering therapy

- Normal SU during gout flare does not exclude the diagnosis of gout.
- Repeat SU ≥2 weeks after resolution of flare if highly suspicious of gout.

No → Other causes of acute monoarthritis - manage accordingly

Yes → **Clinical diagnosis of gout**

Investigations:
- Baseline SU, other blood/urine/imaging study as indicated
- Screening of associated comorbidities

Treatment

Non-pharmacological:
- Topical ice during gout flare
- Health education
- Lifestyle modification
- Avoidance of medications that increase risk of gout, if feasible

Pharmacological:
- Colchicine, **OR**
- NSAIDs/COX-2 inhibitors **OR**
- Corticosteroids **OR**
- Combination of the above

Consider ULT if indicated**

*__ULT is indicated if:__
- recurrent gout flares (≥2 flares in 12 months) **OR**
- presence of tophi **OR**
- presence of radiographic damage due to gout

ULT is conditionally recommended if:
- previously had >1 flare but infrequent (<2 flares/year)
- first gout flare if:
  - concomitant CKD stage ≥3 **OR**
  - SU >540 µmol/L **OR**
  - presence of urolithiasis

Indication for ULT*

Yes →
- Allopurinol as first-line ULT
- Start allopurinol at low dose and uptitrate slowly especially in patients with CKD
- Monitor for drug-related adverse events
- Treat-to-target (T2T) strategy: aim for SU <360 µmol/L
- Do not stop ULT during attack
- Initiate flare prophylactic treatment (at least 3 - 6 months)
- Monitor for associated comorbidities

If unable to tolerate allopurinol/failure to achieve SU target despite dose escalation and good compliance to treatment, consider:
- switching to febuxostat or uricosuric agent
- addition of uricosuric agent

Titrate dose accordingly until SU target is achieved.

No → Continue to monitor for possible indication in future

1. INTRODUCTION

The early records of gout by the Egyptians dated back to 2640 before common era (BCE) and the disease was also described by Hippocrates in the fifth BCE.[Nuki G et al., 2016] Despite being one of the oldest joint diseases, its prevalence and incidence seem to be increasing globally.[Dehlin M et al., 2020] . 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.[Hui M et al., 2017] 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.[Dehlin M et al., 2020] A study in a rheumatology centre in Malaysia reported that only 34.9% of its patients achieved the recommended target serum urate (SU) level. Nonadherence was the main reason for failure to attain the target.[Teh CL et al., 2019]

The first edition of this CPG was published in 2008 by the Malaysian Society of Rheumatology. Since then, there have been advances in understanding 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 the SU to <360 µmol/L, crystals are dissolved and this suggests that gout is potentially a 'curable' disease. However, it is necessary for ULT which is the cornerstone of therapy 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, the damage is permanent.

Of equal significance is the evolving science regarding risk factors e.g. fructose-rich food and obesity. Obesity is thought to be a contributing factor in the rising prevalence and incidence of gout.[Dehlin M et al., 2020] Fructose-rich food increases risk for incident gout. On the other hand, plant-derived high purine diet does not.[Li R et al., 2018] 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, is the role of education for health care professionals, patients and carers. 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.[Spencer K et al., 2012] Therefore an updated version of the CPG is timely.s

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 the 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 an inflammatory joint disease caused by the deposition of monosodium urate (MSU) crystals in synovial joints and other tissues. This is a consequence of persistent hyperuricaemia.

- However not all hyperuricaemic individuals develop MSU crystallisation[Dalbeth N et al., 2015] or gout.[Kapetanovic MC et al., 2018; Dalbeth N et al., 2018; Campion EW et al., 1987]

Although gout is predominantly a musculoskeletal condition, it can also have extra-articular involvement. The clinical manifestations of gout include acute and chronic arthritis, bursitis, tophi, urate nephropathy and urolithiasis.

2.2. Epidemiology

Globally the prevalence of gout ranges from 0.1% to 6.8% while the incidence varies between 0.58 and 2.89 per 1,000 person-years.[Dehlin M et al., 2020] Gout is traditionally a disease of middle-aged and older men. Its occurrence is unusual before the age of 45 years in men[Doherty M, 2009] or premenopausal women.[Hak AE et al., 2010] The prevalence and incidence of gout increases with age, a pattern seen over the entire lifespan in men and after menopause in women.[Dehlin M et al., 2020]

There are no local population-based epidemiologic studies on gout. However, hospital-based studies from a few tertiary centres reported a peak age of gout onset from 30 to 60 years. Patients were predominantly males with a ratio ranging from 8:1 to 12:1. Distribution according to ethnicity was dependent on the region where the studies were conducted. Although majority of the patients were Malays, the Chinese and Indians were also affected.[Wahinuddin S et al., 2019; Teh CL et al., 2013; Mohd A et al., 2011; Mageswaren E et al., 2006] A study in Sarawak showed a preponderance towards the native population which consisted of Malays, Ibans and Bidayuhs.[Teh CL et al., 2013]

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 and has a recognised association with cardiometabolic disorder. Prevention of exposure to risk factors for hyperuricaemia is important not only in gout, but also cardiovascular (CV) disease management.

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
  - Sugar-sweetened soft drinks/ beverages
  - Fruit juice
  ○ Red meat
  ○ Seafood*
• Medications**
  ○ Diuretics
	• Diet
	  ○ Dairy products
	  ○ Soy-based food
	• Vitamin C[$]
	• Medications
	  ○ Losartan
	  ○ Calcium channel blockers
	• Physical activities

○ Non-losartan angiotensin II receptor blockers ○ Angiotensin-converting enzyme (ACE) inhibitors ○ β-blockers ○ Cyclosporine ○ Tacrolimus ○ Pyrazinamide ○ Ritonavir ○ Low-dose aspirin*** • Others ○ CKD ○ Hypertension ○ Psoriasis ○ Haematological malignancies ○ Menopause	
Non-modifiable risk factors	
• Increasing age • Male gender • Ethnicity • Genetic ○ Single nucleotide polymorphism - SLC2A9, ABCG2, SLC17A1, GCKR genes ○ Enzymatic defects in purine metabolism - hypoxanthine-guanine phosphoribosyl transferase deficiency - glycogen storage disease	

*A cohort study showed that fatty fish rich with omega-3 PUFA reduced risk of recurrent gout flares.
**Decision to discontinue a medication should be made based on consideration of its benefits weighed against risks in gout patients.
***Aspirin if taken for appropriate indications should not be discontinued in gout patients as a means of SU reduction.ACR, 2020
$500 mg of vitamin C reduces SU and risk of incident gout but is not statistically effective in urate lowering compared with allopurinol in gout patients.Stamp LK et al., 2013, level I; Choi HK et al., 2009, level II-2

a. Body weight

Excess weight is a major risk factor for developing gout. Men with obesity may not benefit from other modifications unless weight loss is addressed.McCormick N et al., 2020, level II-2

Individuals with body mass index (BMI) ≥30 kg/m^2 were more likely to develop gout compared with those with BMI <30 kg/m^2 (RR=2.24, 95% CI 1.76 to 2.86).Evans PL et al., 2018, level II-2

In various populations:Aune D et al., 2014, level II-2

- 5-unit increment in BMI increased risk of gout with RR=1.55 (95 % CI 1.44 to 1.66)
- when compared with BMI of 20, higher BMI increased 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. Alcohol consumption

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.[Li R et al.,.2018 level II-2]

c. Dietary

A meta-analysis showed that certain foods increased the risk for developing hyperuricaemia and gout when highest quintile intake was compared with lowest quintile intake as shown below:[Li R et al., 2018, level II-2]

Type of food	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 omega-3 polyunsaturated fatty acid derived from fatty fish may override the potential deleterious effect of its high purine content.[Zhang MA et al., 2019, level II-2]

The association of fructose intake and gout in the above meta-analysis was supported by two other meta-analyses:

- High fructose consumption with RR of 1.62 (95% CI 1.28 to 2.03)[Jamnik J et al., 2019, level II-2]
- High intake of sugar-sweetened beverages and high intake of fruit juice 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[Ayoub-Charette S et al., 2019, level II-2]

In the same meta-analysis, purine-rich vegetables did not increase risk for incident gout. Certain foods were shown to lower the risk for developing hyperuricaemia and/or gout:[Li R et al.,.2018 level II-2]

- High vs no dairy product consumption for hyperuricaemia (OR=0.50 95% CI 0.37 to 0.66) and gout (OR=0.56, 95% CI 0.44 to 0.70)
- High vs low soy-based foods consumption for hyperuricaemia (OR=0.70 95% CI 0.56 to 0.88) and gout (OR=0.85 95% CI 0.76 to 0.96)

d. Supplements

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

- In 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).[Juraschek SP et al., 2011, level I]
- Intake of total vitamin C at different doses among male healthcare professionals reduced risk of incident gout compared with men with intake <250 mg/day:[Choi HK et al., 2009, 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)

e. Hypertensive medications

In hypertensive patients, the following antihypertensive drugs increased the risk of incident gout:[Choi HK et al., 2012, 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 RR of 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).[Evans PL et al., 2018, level II-2] As for diuretic class, 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.[Bruderer S et al., 2014, level II-2]

3.2 Preventive Strategies

In a large cohort study on male and predominantly white subjects, population attributable risks (PAR) showed that with more preventive strategies instituted, more incident gout can be prevented:[McCormick N et al., 2020, 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 hyperuricaemia and/or gout:
  - a healthy lifestyle should be advocated, which includes
    - maintenance of a healthy body weight (body mass index <25 kg/m^2)
    - 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

- Fructose-rich diet increases the risk of incident gout.

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

4. NATURAL HISTORY

Gout may progress to a stage with joint damage and tophi if untreated properly with long-term therapy. 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. chronic gouty arthritis

Gout typically presents for the first time with acute monoarthritis (flare) of the foot or ankle. 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 and may involve multiple joints (polyarticular gout), including those of the upper limbs. If hyperuricaemia remains uncontrolled, chronic gouty arthritis 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.

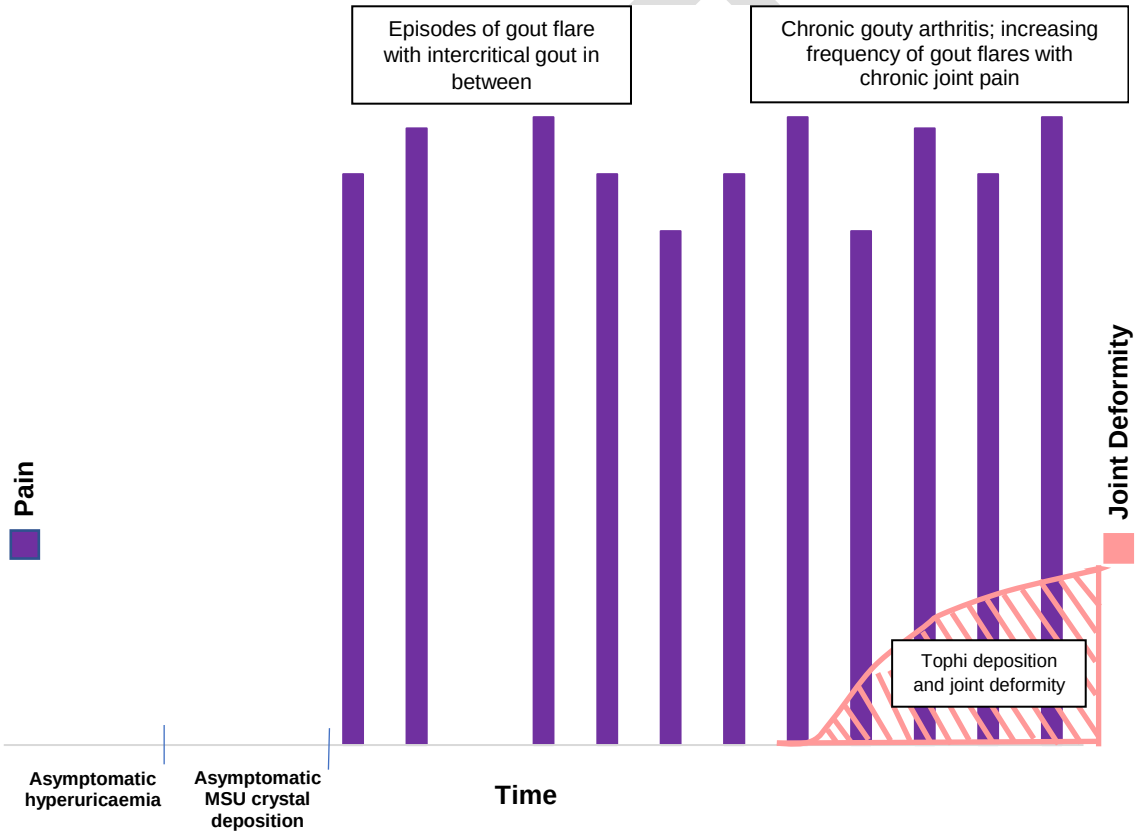

Figure 1: Natural history of gout

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 [Bursill D et al., 2019]
- 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 metatarsophalangeal (MTP) joint (podagra); the foot and ankle are also commonly involved joints
- 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
- 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
  - Commonest affected site is the first MTP joint (podagra); the foot 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 [Bursill D et al., 2019]

5.3 Chronic Gouty Arthritis

- Defined as persistent joint inflammation induced by MSU crystals [Bursill D et al., 2019]
- Characterised by chronic arthritis, tophi or both, with chronic joint pain, functional disability, structural joint destruction and 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
- chronic gouty arthritis, which may be associated with:
  - joint deformity e.g. fixed flexion deformity
  - subcutaneous tophi (refer to **Figure 2** below)
    - appear as white or yellow, non-tender hard nodules but 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

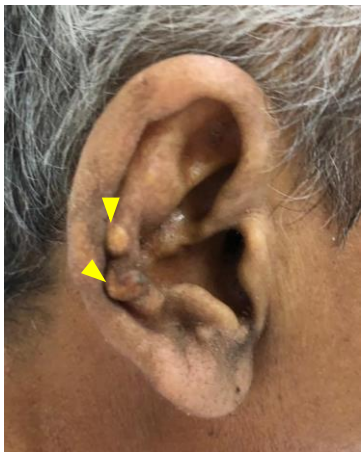

Figure 2a

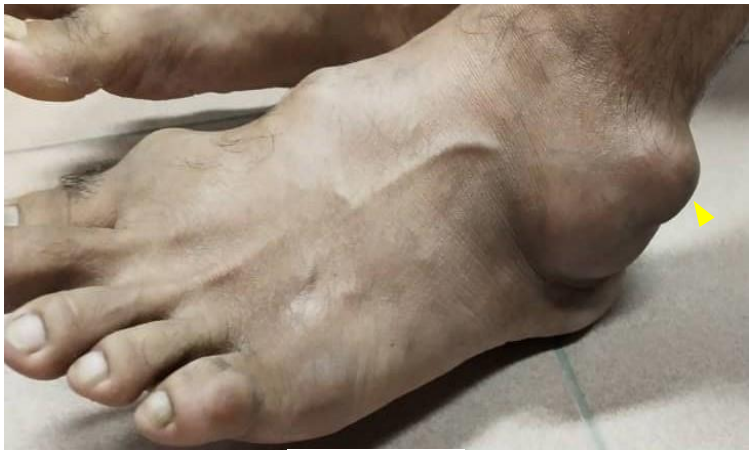

Figure 2b

Photo 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 and can complicate the disease management and outcomes.

A large cohort study determined the risk of comorbidities in patients with gout at diagnosis and follow-up compared with those without gout.[Kuo CF et al., 2014, level II-2]

- At time of 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 and genitourinary diseases were associated with a higher risk for 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) in the 10-year period before gout was diagnosed
- During follow-up after 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)
  - risk of comorbidities incidence increased with a Charlson index ≥1 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% 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 pulmonary disease (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)

  - psoriasis (HR=1.53, 95% CI 1.34 to 1.74)
  - osteoarthritis (HR=1.45, 95% CI 1.35 to 1.54)
- gout was also associated with all-cause mortality with HR of 1.13 (95% CI 1.08 to 1.18)

A meta-analysis showed that gout and hyperuricaemia did not increase the risk of dementia (HR=0.94, 95% CI 0.69 to 1.28).[Pan S-Y et al., 2021, level II-2]

In another 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).[Roughley M et al., 2015, level I]

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).[Francis-Sedlak M et al., 2020, level III]

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 a 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.[Li L et al., 2020, level II-2]

- Patients with uncontrolled gout have a higher association with diabetes mellitus, CKD and congestive heart failure compared with those with good control.

Recommendation 2
- Screening for comorbidities should be done upon diagnosis and follow-up of gout.

7. DIAGNOSIS

Demonstration of MSU crystals in synovial fluid (SF) confirms the diagnosis of gout. If SF examination 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

Demonstration of MSU (negative birefringent) crystals in SF or tophus aspirates is the gold standard in the diagnosis of gout (**Figure 3**). It has 100% specificity. Polarised light microscopy is the standard method for detecting MSU crystals in SF. Low-quality evidence suggested that MSU crystals remained stable in SF stored at room temperature for 24 - 48 hours and should be refrigerated (at 4^{o}Celcius) if analysis was to be delayed.[Graf SW et al., 2013, level III]

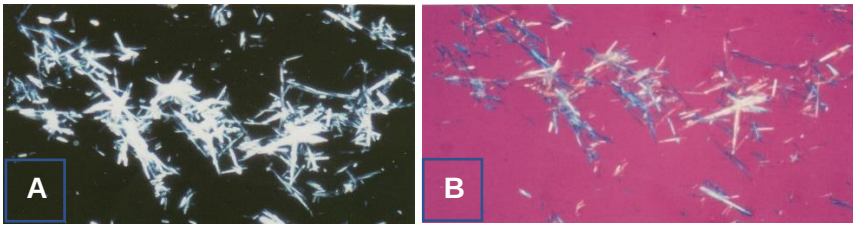

Figure 3: Photos of needle-shaped MSU crystals in SF viewed through A) dark-field microscopy B) polarised microscopy

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 with reference to MSU crystals in the diagnosis of gout.[Sivera F et al., 2014, level III (a)]

Clinical features highly suggestive but not specific for gout:[EULAR, 2018]

- monoarticular involvement of a foot (especially the first MTP) or ankle joint
- previous similar acute arthritis episodes
- rapid onset of severe pain and swelling (at its worst in <24 hours)
- erythema
- associated cardiovascular diseases
- male gender
- hyperuricaemia

7.3 Laboratory Investigations

- Diagnosis of gout should not be made based on hyperuricaemia alone.
- The cut-off SU to diagnose hyperuricaemia based on gender is 7.0 mg/dL (420 µmol/L) for male and 6.0 mg/dL (360 µmol/L) for female.[Li Q et.al., 2019]

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

The risks for both gout incidence in gout-free individuals and recurrence of flares in individuals with preexisting gout increase with higher SU levels at baseline.[Shiozawa A et.al., 2017, 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 increased risk of developing gout (dose-dependent).[Dalbeth et al., 2018, level II-2]

- 6.0 - 6.9 mg/dL (360 - 414 µmol/L) with HR of 2.7 (95% CI 2.0 to 3.6)
- 7.0 - 7.9 mg/dL (420 - 474 µmol/L) with HR of 6.6 (95% CI 5.0 to 8.8)
- 8.0 - 8.9 mg/dL (480 - 534 µmol/L) with HR of 15 (95% CI 11 to 20)
- 9.0 - 9.9 mg/dL (540 - 594 µmol/L) with HR of 30 (95% CI 21 to 42)
- ≥10 mg/dL (≥600 µmol/L) with HR of 64 (95% CI 43 to 96)

- 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:

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

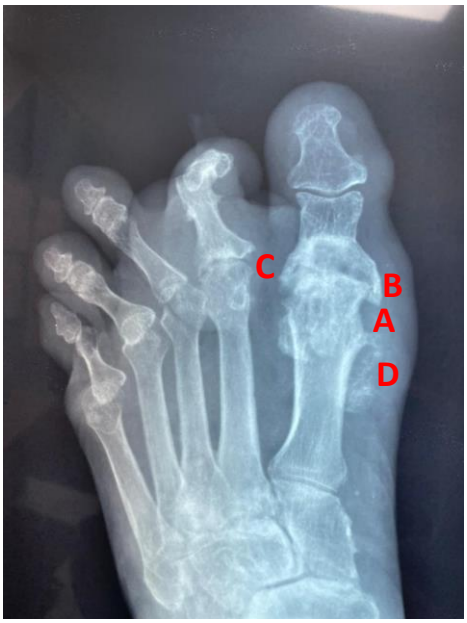

Figure 4a: AP radiograph of left foot

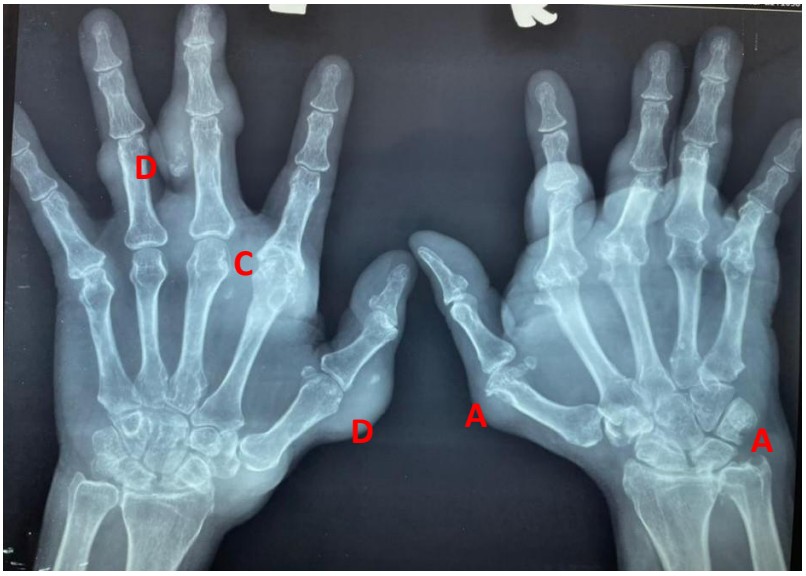

Figure 4b: AP radiograph of both hands

b. Ultrasonography

Musculoskeletal ultrasonography is useful to assist the diagnosis of gout especially when presentation is atypical or 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.[Sivera F et al., 2014, level III (a)]

- A meta-analysis of three diagnostic studies on ultrasound joint/location-based evaluations gave a sensitivity of 0.71 (95% CI 0.64 to 0.78), a specificity of 0.62 (95% CI 0.56 to 0.67) and an AUC of 0.8549 for DCS in the diagnosis of gout.[Zhang Q et al. 2018, level]

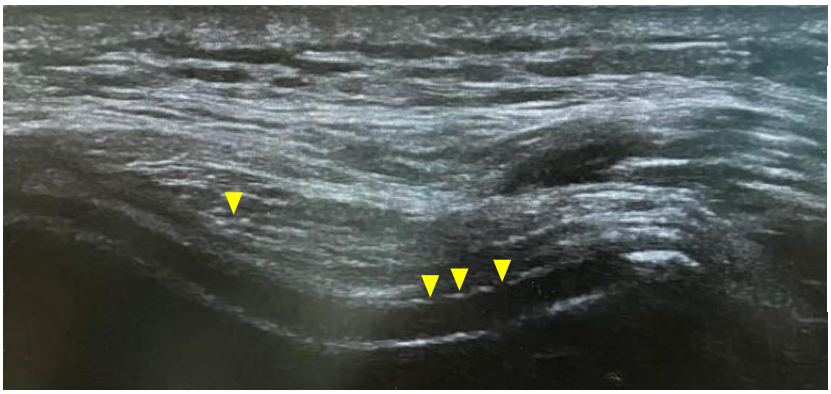

Figure 5: Suprapatellar transverse ultrasound scan of right knee demonstrating double contour sign indicated by arrow heads.

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 in the diagnosis of gout.[Yu Z et al., 2018, level III] However, this imaging modality is not utilised as a diagnostic tool for gout as it is not widely available in Malaysia.

Recommendation 3

- Synovial fluid aspiration of an affected joint should be performed to examine for the presence of monosodium urate crystals to confirm the diagnosis of gout.
  - If aspiration is not feasible, the diagnosis may be made based on clinical manifestations.

8. DIFFERENTIAL DIAGNOSES AND BASELINE INVESTIGATIONS

Gout commonly presents with acute monoarthritis. A diagnosis of gout can be reasonably made in a hyperuricaemic patient who presents with acute monoarthritis of the first MTP joint. Other causes of acute monoarthritis should be considered before making a diagnosis of gout.

The main differential diagnoses of gout 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
   - 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 psoriatic skin lesions, nail dystrophy (e.g. pitting, onycholysis or crumbling)

iv. reactive arthritis
   - recent urethral or bowel infection
   - presence of urethral discharge or ulcer, rash on soles, conjunctivitis

Baseline blood investigations (full blood count, renal profile, liver function test/aspartate transaminase, SU) and radiological tests are performed to support the diagnosis of gout and identify concomitant comorbidities. Screening for metabolic syndrome should also be done.

9. TREAT-TO-TARGET

Achieving SU target over time leads to suppression of gout flares and tophi size.

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:[Doherty M et al., 2018, 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 in gout patients, comparing allopurinol dose escalation using T2T strategy aiming for SU <6 mg/dL (360 µmol/L) and control (CrCl-based allopurinol dose), the final SU reduction was greater in the dose escalation group with a MD of 1.2 mg/dL (72 µmol/L) (95% CI 0.67 to 1.5) at 12 months. However, there were no significant differences in episodes of gout flares and change in tophus size in both groups. There were also no significant differences in renal function changes and SAEs.[Stamp LK et al., 2017, level I (a)]

A large cohort study on Korean adults showed that the lowest and highest SU categories were associated with all-cause mortality:[Cho SK et al., 2018, level II-2]

- Lowest SU category vs 6.5 - 7.4 mg/dL (390 - 444 µmol/L) 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 6.5 - 7.4 mg/dL (390 - 444 µmol/L) 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 1.10 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.[ACR, 2020; EULAR 2016; BSR, 2017] The CPG DG opines that this target should be used in all gout patients.

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). On the other hand, prolonged SU level <3 mg/dL (180 µmol/L) is not recommended.[EULAR, 2016]

Recommendation 4

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

- **Discontinuation of ULT**

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.[Beslon et al., 2017, level II-2]

One of the cohort studies included in the systematic review showed that higher SU level during ULT treatment (HR=1.57, 95% CI 1.18 to 2.08) and follow-up after ULT discontinuation (HR=2.29, 95% CI 1.91 to 2.74) was independently associated with gout recurrence. On the other hand, another study demonstrated that higher BMI, earlier age at onset of gout, higher SU level and longer duration of ULT before discontinuation were not significantly associated with gout recurrence.[Beslon et al., 2017, level II-2]

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

10. TREATMENT

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

10.1 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 adherence to treatment 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, decrease of at least 2 mg/dL (120 µmol/L) in SU, achievement of SU <5 mg/dL (300 µmol/L), reduction of tophi at two years etc. These findings were also supported by three cohort studies included in the review. GRADE assessment of the evidence showed a rating of low to moderate quality.[Ramsubeik K et al., 2018, level I]

Health education is strongly recommended as part of gout management. It consists of education on:[ACR, 2020; BSR, 2017; EULAR, 2016]

- 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 follow-up, weight loss (3 - 34 kg) in overweight/obese gout patients was associated with:[Nielsen SM et al., 2017, 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:[Zhang Y et al., 2012, level II-2]

- acute intake of total purine in the highest quintile (median=3.48 g) increased risk of recurrent gout flares by almost five times compared with the lowest quintile (median=0.85 g) over a 2-day period (OR=4.76, 95% CI 3.37 to 6.74); with a significant trend of higher risk in increasing quintile
- with 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)
- with 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.[Neogi T et al., 2014, 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).
- ~~Analysis of alcohol types showed a significant trend of increasing consumption for wine, beer or liquor with risk of recurrent gout flares.~~

*One typical drink contains approximately 15 grams of alcohol.

- **Omega-3 polyunsaturated fatty acids**

Omega-3 polyunsaturated fatty acids (n-3 PUFA) had been shown to have anti-inflammatory effects through rapid and selective inhibition of the NLRP3 inflammasome.[Calder PC, 2013; Yan Y et al., 2013; Serhan CN et al., 2008; Martinon F et al., 2006] 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:[Zhang M et al., 2019, level II-2]

- dietary n-3 PUFA-rich fish consumption of ≥2 servings 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[Kirakosyan A et al., 2009; Seeram NP et al., 2001; Wang H et al., 1999] that possess anti-inflammatory and antioxidant properties.[Schlesinger N et al., 2010; Kelley DS et al., 2006; He YH et al., 2006; Seeram NP et al., 2001] A case-crossover study on gout showed that compared with no intake, the risk of gout flares was decreased by:[Zhang Y et al., 2012, 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 use, risk of gout flares was 75% lower than periods without either exposure (OR=0.25, 95% CI 0.15 to 0.42).

- **Others**

ACR recommends to limit high-fructose corn syrup intake for patients with gout, regardless of disease activity.[ACR, 2020] Medications that increase risk for gout should be discontinued or replaced with alternatives if possible. Refer to **Table 1** on **Risk factors for gout.** Gout patients are advised to stay well hydrated, cease smoking and exercise to achieve physical fitness.[ACR, 2012]

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:
    - weight reduction in those who are obese/overweight
    - limitation of intake of purine-rich food especially of animal origin except omega-3 polyunsaturated fatty acid-rich fish
    - limitation of intake of all types of alcohol (beer, wine and liquor)
    - limitation of intake of high-fructose corn syrup
  - avoidance of medications that increase risk of gout if feasible

c. 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 with a MD of -3.33 (95% CI -5.84 to -0.82). Although ice packs reduced swelling, difference between the groups was not significant.[Moi JHY et al., 2013, level I]

The affected joints in gout flare should be rested, elevated and exposed in a cool environment.[BSR, 2017] Ice packs can be used as adjuvant treatment.[ACR, 2020; BSR, 2017]

- 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.

10.2 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 cardiovascular events.

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

An observational study showed that not all patients with hyperuricaemia will develop gout. Only 20% of patients with SU >9.0 mg/dL (540 µmol/L) will do so in five years.[Campion et al., 1987] Two more recent studies showed similar results with the following findings:

- the absolute risks for 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[Kapetanovic MC et al., 2018, level II-2]
- 15-year cumulative incidence ranged from 1.1% (95% CI 0.90 to 1.4) for baseline SU <6 mg/dL (360 µmol/L) to 49% (95% CI 31 to 67) for ≥10 mg/dL (600 µmol/L)[Dalbeth et al., 2018, level II-2]

In an RCT on patients with CKD stage 3 patients and asymptomatic hyperuricaemia, the incidence of gouty arthritis was lower in febuxostat compared with placebo group (p=0.007). However, the incidence rates of gouty arthritis in both arms were low (0.91% and 5.86% for febuxostat and placebo respectively).[Kimura K et al., 2018, level I] Therefore, the benefit of starting ULT in these patients may not outweigh the potential adverse events of treatment as the vast majority of 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 mg/dL). The quality of the primary papers included was moderate.[Bose B et al., 2014, level I]

An RCT involving type 1 diabetic patients with kidney disease (mean SU of 362 µmol/L) also revealed nonsignificant difference in the decline of iohexol-based GFR between the allopurinol and placebo groups after three years of treatment.[Doria A et al., 2020, level I] The quality of the RCT was moderate.

In one RCT among CKD stage 3 patients and asymptomatic hyperuricaemia (SU levels ≥416 µmol/L), there was nonsignificant difference in mean eGFR slope between febuxostat and placebo groups.[Kimura K et al., 2018, 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 ≥416 µmol/L) and ≥1 risks of cardiovascular, cerebral or renal disease.[Kojima S et al., 2019, 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 group. In febuxostat group, there was an increase in eGFR in CKD 3 only and decrease in eGFR in CKD stage 4 and 5. The differences between the groups were significant in CKD stage 3 and 4 but nonsignificant in CKD stage 5.[Liu X et al, 2019, level II-1]

In terms of safety, the above meta-analysis showed no significant difference in skin rash between allopurinol and placebo group.[Bose B et al., 2014, level I] There was also no significant difference in SAEs among patients with type 1 diabetic kidney disease. However, there were numerically more fatal SAEs in allopurinol arm.[Doria A et al., 2020, level I] There was no significant difference in AEs between febuxostat and placebo[Kimura K et al., 2018, level I] or febuxostat and allopurinol.[Liu X et al., 2019, level II-1]

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

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

An RCT compared febuxostat and non-febuxostat (allopurinol or placebo) treatment in elderly patients (≥65 years old) with asymptomatic hyperuricaemia (SU levels ≥416 µmol/L) and ≥1 risks of CV, cerebral or 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).[Kojima S et al., 2019, 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.[Gois PHF et al., 2020, 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.[Xu H et al., 2021, level I]

In terms of safety, no AEs were reported but the occurrence of malignant tumours and venous thrombosis were similar in the febuxostat and non-febuxostat groups.[Kojima S et al., 2019, level I.] There were also inconclusive results regarding the occurrence of AEs between those who received ULTs and placebo.[Gois PHF et al., 2020, level I]

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

10.3 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). Established guidelines suggest lowering SU level to <360 µmol/L.[ACR, 2020; EULAR, 2016]

- Traditionally, it was recommended that ULT is initiated after resolution of gout flare. However, ACR recently recommended that ULT can also be initiated during gout flare.[ACR, 2020]

- **Indications of urate-lowering therapy**

- ACR, EULAR and BSR recommend the initiation of ULT for gout patients with:[ACR, 2020; BSR, 2017; EULAR, 2016]
  - 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 first gout flare with the following indications:[ACR, 2020]
- with comorbid 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 have previously experienced >1 flare but have infrequent flares (<2/year).[ACR, 2020]

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:[Seth R et al., 2014, 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 target between allopurinol and benzbromarone
- allopurinol 100 - 300 mg daily had fewer patients achieving 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 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.

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.[Eminaga F et al., 2016, level I]

Allopurinol has been associated with several AEs. Most are mild gastrointestinal events. The most serious AE is severe cutaneous adverse reaction (SCAR) which can be fatal.[Stamp LK et al., 2012, 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.[Ng CY et al., 2016, level I; Stamp LK et al., 2012, level II-2]

A case-control study demonstrated a relationship between allopurinol starting dose and AHS. The median time from starting allopurinol to AHS was 30 days (range 1 - 1080 days) and 90% of AHS cases occurred within the first 180 days. There was strong dose-response relationship between starting dose of allopurinol [adjusted for estimated glomerular filtration rate (eGFR)] and risk of AHS (p=0.001). AHS cases:
- had started allopurinol at a higher dose (p<0.001)
- were more likely to have an allopurinol starting dose higher than creatinine clearance (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.[Stamp LK et al., 2012, level II-2] This would translate to a starting dose of allopurinol 100 mg daily in those with normal renal function.

Two systematic reviews on gout showed no significant difference in any AEs between allopurinol (up to 300 mg daily) and:
- placebo[Seth R et al., 2014, level I]

- febuxostat (40 and 240 mg daily)[Castrejon I et al., 2015, level I; Seth R et al., 2014, 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).[Seth R et al., 2014, level I]

In the Cochrane systematic review, there was also no significant difference in AEs between allopurinol (100 - 600 mg), benzbromarone (100 mg daily) and probenecid (2 g daily).[Seth R et al., 2014, level I] Quality of the primary papers in both reviews varied from low to high.[Castrejon I et al., 2015, level I; Seth R et al., 2014, level I]

HLA-B*58:01 is an allele that is carried mostly by the Han Chinese, Korean and Thai people. It is strongly associated with SCAR (OR=44.0, 95% 21.5 to 90.3). The gene dosage effect (heterozygotes vs homozygotes) of HLA-B*58:01 influences the development of allopurinol-induced cutaneous adverse drug reactions [OR of 15.3 (95% CI 8.4 to 27.7) for HLAB*58:01 heterozygotes and 72.5 (95% CI 14.7 to 356.7) for homozygotes]. Both HLA-B*58:01 and renal impairment increase the risk of allopurinol-induced cutaneous adverse drug reactions. The OR for SCAR for heterozygous HLA-B*58:01 and normal renal function is 15.3 (95% CI 8.4 to 27.7) and for homozygous HLA-B*58:01 and severe renal impairment is 1269.5 (95% CI 192.3 to 15,260.1).[Ng CY et al., 2016, level I]

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.[Chong HY et al., 2017] 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. Results from a Cochrane systematic review of 4 RCTs showed results of the following comparisons:[Tayar JH et al., 2012, level I]

- febuxostat vs placebo
  - febuxostat was more likely to achieve SU levels <6.0 mg/dL (360 µmol/L) at different study end-points of different RCTs
    - 40 mg at 4 weeks (RR=40.1**,** 95% CI 2.5 to 639.1)
    - 80 mg at 28 weeks (RR=68.9, 95% CI 13.8 to 343.9)
    - 120 mg at 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 differences 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) with RR of 1.8 (95% CI 1.6 to 2.2) at 24 - 52 weeks, 2.2 (95% CI 1.9 to 2.5) at 28 - 52 weeks and 2.30 (95% CI 1.94 to 2.73) at 28 weeks respectively

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 CV safety of febuxostat. To fulfill the requirement of the United States (US) Food and Drug Administration (FDA), a large RCT [Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout (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.[White WB et al., 2018, level I] However, there was a high but similar dropout rate in the two

groups.

FDA had issued a black box warning regarding the increased rate of CV death of febuxostat in gout patients with established CV disease.

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 European Medicines Agency, febuxostat was noninferior to allopurinol with regards to the occurrence of major CV outcomes (primary outcome of hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome, non-fatal 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.[Mackenzie S et al., 2020, level I]

Approximately one-quarter of patients with gout have CKD stage 3 and above.[Roughley MJ et al., 2015] 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/minute), febuxostat (40 mg and 80 mg, either extended release or immediate release) was more effective than placebo in achieving a 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 flare 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.[Saag KG et al., 2019, level I]

- **Uricosuric agents**

In a Cochrane systematic review on uricosuric agents in chronic gout, the following results were demonstrated:[Kydd ASR et al., 2014, level I]

- comparison between benzbromarone and allopurinol showed no significant difference in SU normalisation and AEs
- benzbromarone was more effective than probenecid in SU normalisation 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 (RR= -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. [BSR, 2017; EULAR, 2016; ACR, 2012]

- **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.[Sundy JS et al., 2011, level I] ACR recommends pegloticase in chronic gouty arthritis patients for whom treatment with xanthine oxidase inhibitor, 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.[ACR,2020] However, its use is limited because of its cost.

- Health care professionals should be aware of the potential severe AEs of allopurinol especially severe cutaneous adverse reactions 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 creatinine clearance.
- Routine screening of HLA-B*58:01 prior to commencement of allopurinol is not recommended locally.

Recommendation 7
- Patients with gout should be treated with urate-lowering therapy.
  - Allopurinol is the first-line therapy.
  - When allopurinol is contraindicated or not tolerated, febuxostat or uricosuric agents can be considered.

b. Gout flare

Gout flare is an extremely painful condition and can be very disabling. The pain needs to be assessed objectively using a validated tool e.g. VAS and then, treated promptly and adequately. The mainstay of treatment is analgesia.

- **Colchicine**

In a Cochrane systematic review of two RCTs, low dose (1.2 mg stat, then 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:[van Echteld I et al., 2014, level I]
  - low dose colchicine vs placebo
    - 32 to 36 hours (RR=2.43, 95% CI 1.05 to 5.64; NNTB of 5, 95% CI 2 to 20)
  - high dose colchicine vs placebo
    - 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 at 32 to 36 hours.

There was no significant difference in gastrointestinal (GI) adverse events (AEs) e.g. diarrhoea, vomiting or nausea between low dose colchicine and placebo. However, high dose colchicine caused more GI AEs than:[van Echteld I et al., 2014, 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 RCT 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 significant less AE compared with indomethacin. Quality of the primary papers was low to moderate.[van Durme CMPG et al., 2014, 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 with Patient Global Assessment (PGA). Etoricoxib also had fewer drug-related AEs (RR=0.64, 95% CI 0.50 to 0.81) with no significant

difference in serious AEs.[Zhang S et al., 2015, 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 IM diclofenac (75 mg) plus indomethacin (50 mg TDS for two days then 25 mg TDS for three days) at two weeks. However, there was significantly more AEs in the diclofenac plus indomethacin-treated patients. Quality of the RCT was moderate.[Janssens HJ et al., 2008, level I]

Two other systematic reviews showed no significant difference in pain scores[Billy CA et al., 2018, level I] and mean pain reduction[van Durme CMPG et al., 2014, 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.[Billy CA et al., 2018, level I, van Durme CMPG et al., 2014, level I]

- **Interleukin-1 inhibitor**

A systematic review comparing IL-1 inhibitors with corticosteroids showed canakinumab had better effectiveness than intramuscular (IM) triamcinolone acetonide 40 mg at 72 hours in:[Sivera F et al., 2014, level I (b)]

- 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)
- better 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[BSR, 2017] depending on the severity of flares.[EULAR, 2016]

Recommendation 8

- In gout flare, the following monotherapy may be used*:
  - low dose colchicine
  - nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors
  - corticosteroids
  - combination of the above if monotherapy response is insufficient

*The choice of drug will be guided by patient's comorbidities.

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.[Seth R et al., 2014, 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 two RCTs, severity of the flares based on VAS was also significantly lower.
- In another RCT of low risk of bias, a single dose of canakinumab ≥50 mg or 4-weekly doses provided significant prophylaxis against flares compared with daily colchicine 0.5 mg.

In the fourth RCT of high risk of bias, colchicine 1 mg/day given for 7 - 9 months or 10 - 12 months was 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 RCTs included in the review.

Alternative method to reduce gout flare is a stepwise dose increase of ULT. In an RCT, stepwise dose increase of febuxostat and 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. There were no differences in AEs identified between the three groups.[Yamanaka H et al., 2018, 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 than corticosteroids in flare prophylaxis. Both prophylactic agents were well tolerated.[Yu J et al., 2018, level III]

CPG DG opines that stepwise dose increase of ULT and/or concomitant colchicine should be the preferred method for gout flare prophylaxis. If colchicine is contraindicated, corticosteroids may be used with caution. 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.
  - If colchicine is contraindicated, corticosteroids may be used with caution.

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.[Doherty M et al., 2018, level I; Stamp LK et al., 2017, level I(a); Stamp LK et al., 2017, level I(b)]

Allopurinol is effective and safe in gout patients with CKD.[Doherty M et al., 2018, level I; Stamp LK et al., 2017, level I(a); Stamp LK et al., 2017, level I(b)] It is the preferred first-line ULT in gout patients with moderate to severe CKD (stage ≥3).[ACR, 2020] Initiation dose is lower than that used in patients with normal renal function[Stamp LK et al., 2012, level II-2] and subsequent dose escalation is more gradual.

Febuxostat is also effective and safe in gout patients with CKD.[Saag KG et al., 2019, level I] It is the second-line ULT in moderate to severe CKD.[ACR, 2020] 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).[FDA; MIMS]

All uricosurics are contraindicated in gout patients with urolithiasis. ACR does not recommend uricosurics in moderate to severe CKD[ACR, 2020] However, BSR recommends benzbromarone in mild-to-moderate CKD.[BSR, 2017]

- **Gout flare**

Colchicine should be avoided in severe CKD as its safety in this group has not been established.[EULAR, 2016] NSAIDs should also be avoided in CKD due to its potential nephrotoxic

effect.[MoH CKD, 2018] Corticosteroids may be used in gout flares with severe CKD.[BSR, 2017] 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.[Doherty M et al., 2018, level I]

Colchicine at a reduced dose is a recommended prophylaxis treatment in gout patients with CKD.[EULAR, 2016] If colchicine is contraindicated, corticosteroids may be used with caution[Yu J et al., 2018, level III] Avoid NSAIDs in CKD due to its potential nephrotoxic effect.[MoH CKD, 2018]

- The presence of CKD in gout requires a lower starting dose of allopurinol and slower escalation of the dose.
- The maximum dose of allopurinol in gout with CKD should be determined by its tolerability and not renal function.[Graf SW et al. 2015]

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 and important points in the ACR guidelines. Some of the recommendations put forward are extrapolated from evidence not directly on gout. Topical ice is safe for gout flare in pregnant patients.

Colchicine may be used in pregnancy and breastfeeding in 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 placenta at low to moderate doses unlike the latter.[ACR, 2020]

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.[FDA(b)]

There is inadequate data on the use of allopurinol, febuxostat, probenecid and benzbromarone in pregnancy.

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

11. 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 an eight-week small RCT, modest dosage of vitamin C (500 mg/day) was not clinically significant in urate lowering effect compared with allopurinol in gout.[Stamp LK et al., 2013, level I]

- **Fibrates**

In a meta-analysis of six RCTs on type 2 diabetes mellitus and hyperlipidemia with mostly normal urate level, fibrate reduced plasma uric acid concentration compared with placebo (WMD= -1.50 mg/dL, 95% CI -2.38 to -0.63 mg/dL). Subgroup analysis showed that only fenofibrate was effective but not bezafibrate.[Derosa G et al., 2015, level I] The included primary papers had 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.[Jung JY et al., 2018, level III]

- **Statins**

A meta-analysis on patients with dyslipidemia showed atorvastatin increased SU level compared with fenofibrate (MD=1.48 mg/dL, 95% CI 0.88 to 2.08 mg/dL).[Takagi H et al., 2012, level I] The primary papers were of low quality.

In a more recent meta-analysis in patients with hypercholesterolemia and coronary heart disease (CHD), statins reduced plasma uric acid 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.[Derosa G et al., 2016, 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 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.[Saito J et al., 2010, level I]

As for the types of urine alkalinisation, an RCT on primary gout patients 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.[Xue X et al., 2020, level I]

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

12. 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 patients should be concomitantly screened for associated comorbidities.

12.1 Clinical outcomes

The following clinical parameters should be monitored:

- gout flares
- number and size of tophi
- joint damage

12.2 Treat-to-target strategy

The following tests are to be done four weekly while titrating the ULT dose until the SU target is achieved and subsequently can be performed six monthly.

- **Serum urate**

SU is the key parameter in monitoring disease control in accordance with the treat-to-target strategy.[Doherty M et al., 2018, level I, Stamp LK et al. 2017, level I]

- **Renal function test/profile**

Renal function test/profile (RP) is monitored in parallel with SU measurement as it influences therapeutic decisions as mentioned in **Subchapter 10.3**.

12.3 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 reaction.

- 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.[Standard Chem & Pharm Co, 2017]

Refer to **Table 2** for investigations that are done periodically for drug monitoring.

Table 2. Summary of investigations for drug monitoring and screening of cardiovascular risks and comorbidities associated with gout during follow-up

<table>
<tr><th>Investigation</th><th>Allopurinol</th><th>Febuxostat</th><th>Probenecid</th><th>Benzbromarone</th><th>Colchicine</th></tr>
<tr><td>Full blood count (FBC)</td><td rowspan="2">Four weekly during dose titration and then six monthly when dose is stable</td><td rowspan="2">Four weekly during dose titration and then six monthly when dose is stable</td><td rowspan="2">Four weekly during dose titration and then six monthly when dose is stable</td><td>Annually</td><td rowspan="2">Three monthly</td></tr>
<tr><td>Liver function test (LFT/AST)</td><td>Four weekly for first six months and then three monthly</td></tr>
<tr><td>SU and RP</td><td colspan="5">Four weekly until SU <360 µmol/L then six monthly</td></tr>
<tr><td>Fasting Blood Sugar, Fasting Serum Lipid, Haemoglobin A1c (HbA1c), Thyroid function test (TFT)</td><td colspan="5">To be done when gout is first diagnosed and repeated at least once a year</td></tr>
<tr><td>Full and Microscopic Examination of</td><td colspan="5">During clinical review</td></tr>
</table>

Urine (Urine FEME)	
Plain radiography of affected joints Ultrasound of the kidneys, ureters and bladder (USG KUB)	To be done when gout is first diagnosed and repeated when indicated
Electrocardiogram (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 tests, especially serum urate
- Screening for associated comorbidities should be done upon diagnosis and follow-up.

*Refer to above text and table.

13. REFERRAL

Gout is the most common inflammatory arthritis globally[Dehlin M et al., 2020] with the majority of patients managed in primary and general medical healthcare facilities.[Krishnan E et al., 2008] The benefit of understanding the entire patient and associated co-morbidities enables the family care providers to have a holistic approach in treating gout and other associated complicated diseases.[Rimler E et al., 2016] 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 in the box below.[Khanna D et al., 2012]

a. Referral criteria for rheumatology care

1. Diagnostic indication
   a. Diagnosis is uncertain in cases with atypical clinical presentations

2. Therapeutic indication
   a. Refractory to conventional therapy
      i. Gout flare that fails to resolve despite treatment as recommended by the CPG
      ii. Recurrent flares although SU target of <360 µmol/L is achieved
      iii. Difficulty in reaching SU target of <360 µmol/L after a trial of maximum tolerated dose of allopurinol

iv. Tophaceous gout with progressive joint damage, active symptoms or growing tophi despite medical treatment
b. Complicated gout with destructive joint changes
c. Hypersensitivity or intolerance to allopurinol

3. Special group indication
   a. Gout in pregnancy
   b. Gout in CKD stage 3 and above
   c. Suspected gout in premenopausal women or men at age <30 years without predisposing risk factors for gout

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.[Doherty M et al., 2018] However, surgical intervention may be considered when there is uncontrolled infection, entrapment neuropathy or risk of permanent joint destruction.[Kasper IR et al., 2016, level III]

b. Referral criteria for surgical/orthopaedic care

1. Current or impending debilitating complications of tophaceous deposits
   a. Uncontrolled infection
   b. Discharging sinus
   c. Ulceration with risk of infection
   d. Entrapment neuropathy e.g. carpal tunnel syndrome at the wrist
   e. Major joint destruction
   f. Joint instability
   g. Impaired joint motion that affects activities of daily living, work or safety
   h. Functional impairment e.g. the inability to wear shoes or clothing

2. 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

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

Patients with urolithiasis should be assessed by a urologist/surgeon.

Recommendation 12

- Referral of gout patients to a rheumatologist may be considered for the following indications:
  - unclear diagnosis
  - ineffective conventional therapy
  - destructive joint changes
  - allopurinol hypersensitivity or intolerance
  - early onset (<30 years old) without risk factors
  - onset before menopause
  - pregnancy
  - chronic kidney disease stage 3 and above
- 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 an urologist/surgeon.

14. 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.

14.1 Facilitating and Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:
- availability of CPG to healthcare providers (hardcopies and softcopies)
- regular seminar/conference/course for healthcare 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

14.2 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 on gout to improve the understanding of the disease and importance of adherence to treatment. 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.

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

- Percentage of incident gout patients started on ULT* = $\frac{\text{Number of incident gout patients started on ULT in a year}}{\text{Number of incident gout patients in a year}}$ x 100%

*Gout patients who are indicated for ULT are those with either:
  - recurrent gout flares (≥2 flares in 12 months)
  - presence of tophi
  - presence of radiographic damage due to gout

- Percentage of incident gout patients who achieve SU level <360 µmol/L = $\frac{\text{Number of incident gout patients who achieve SU level <360 µmol/L in a period}}{\text{Number of incident gout patients in the same period}}$ x 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. ((antiinflammatory or anti-inflammatory or anti inflammatory) adj 1 agents).tw.
49. (antiinflammatory or anti-inflammatorie* or anti inflammatory*).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 (340 ml)
Malt liquor (7%)	8 - 9 fl oz (230 - 255 ml)
Wine (12%)	5 fl oz (140 ml)
Distilled spirits (40%) ○ Gin, rum, tequila, vodka, whiskey, etc.	1.5 fl oz (40 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. 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	4 - 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
Fruits	4 - 5	1 medium fruits ¼ cup dried fruit ½ cup fresh, frozen or canned fruit ½ cup fruit juice	Apples, bananas, dates, grapes, oranges, mangoes, melons, pineapples, raisins, strawberries, tangerines, guava, papaya
Low-fat/Skim milk and dairy products	2 - 3	1 cup milk or yogurt 1 slice cheese	Skim 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	4 - 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
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: 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)

C. DIETARY RECOMMENDATIONS FOR GOUT

Food To Be Discouraged in Gout	Food To Be Encouraged in Gout

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)
• High-purine supplements (e.g. spirulina, yeast)
	n-3 PUFA-Rich Fish
	• Anchovies
	• Mackerel (ikan kembung, tenggiri, makarel)
	• Herring (ikan parang)
	• Sardines (ikan sardin, tamban)
	• Salmon
	• Trout
	• Tuna (ikan tongkol)
	• Ikan cencaru

Fructose/Sugar • Sugar-sweetened beverages • Fruit juices • Corn syrup • Honey • Sugars, syrups, sweets • Desserts • Processed tomato sauce and chili sauce • Fruit jam	Vegetables Fresh fruits
Alcoholic beverages (e.g. beer, wine, liquor)	Soy-based foods
	Others: Low fat dairy products

References:

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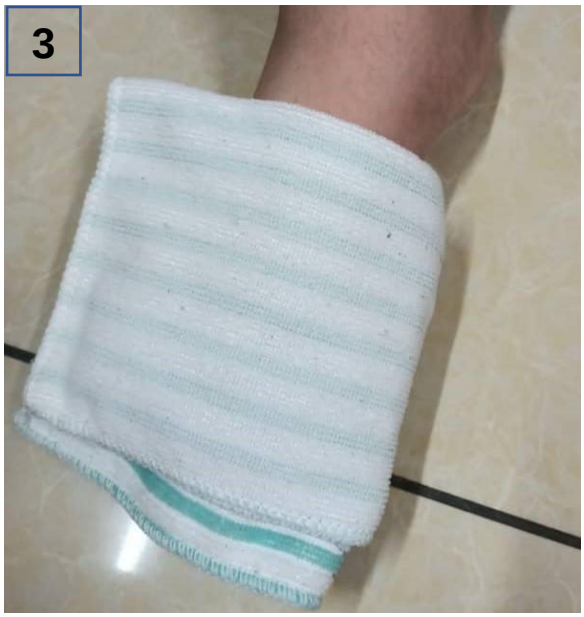
Appendix 4

ICE PACKS APPLICATION

Use of ice pack for gout flare affecting first toe.

Wrap towel around ice pack.



Place wrapped ice pack around affected joint.

Appendix 5

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 modification 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>
*More rapid titration e.g. every 2 weeks is possible, although this needs to be balanced against the increased risk of adverse effects
</td>
<td>
Common:
• Dermatologic
Maculopapular rash, pruritus
• Gastrointestinal
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
• Hematologic
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*
	**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 • **Gastrointestinal** Nausea, vomiting **Serious:** • **Dermatologic** SJS • **Hematologic** 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 sulfonylurea • **Most beta-lactam antibiotics** Increases level of beta-lactam antibiotics
Febuxostat	**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	**Common:** • **Dermatologic** Rash • **Gastrointestinal**	**Contraindications:** • Hypersensitivity to febuxostat	• **Azathioprine/ mercaptopurine** Increased plasma

<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 renal impairment:
<table>
<tr><th>CrCl (ml/min)</th><th>Dose</th></tr>
<tr><td>≥30</td><td>No adjustment</td></tr>
<tr><td><30</td><td>Maximum dose 40 mg OD</td></tr>
</table>
Dosage modifications in hepatic impairment:
<table>
<tr><th>Child-Pugh class</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>Diarrhea, 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.
• 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.</td>
<td>• Concomitant use of azathioprine/ mercaptopurine due to increase in toxicity</td>
<td>concentrations result in severe toxicity of azathioprine and mercaptopurine
• Methotrexate
May enhance hepatotoxic effect of methotrexate
• Theophylline
May increase serum concentration of theophylline</td>
</tr>
<tr>
<td>Benzbromarone</td>
<td>Doses of 50 - 200 mg daily may be used
Usual dose of benzbromarone is 50 - 100 mg/day
Maintain adequate fluid intake (2 - 3 L/day) if not on medically advised fluid restriction diet</td>
<td>Common:
• Gastrointestinal
GI effect e.g. nausea, vomiting, diarrhoea
• Hepatic
May cause liver damage</td>
<td>Contraindications:
• Severe or moderate renal impairment
• Urolithiasis</td>
<td>• Warfarin
May increase effect of warfarin</td>
</tr>
<tr>
<td>Pegloticase</td>
<td>IV infusion 8 mg every 2 weeks</td>
<td>Common:
• Dermatologic
Urticaria
• Gastrointestinal</td>
<td>Contraindications:
• Hypersensitivity to pegloticase
• G6PD deficiency</td>
<td>Discontinue use of oral ULT agents prior to pegloticase therapy and do not initiate during the</td>
</tr>
</table>

Drug	Recommended dose	Possible AEs	Contraindication/ Caution	Common drug interaction*
		Constipation, nausea, vomiting **Serious:** • Infusion-related reaction • **Hematologic** Glucose-6-phosphate dehydrogenase deficiency anaemia • **Cardiovascular** Congestive heart failure **Black Box Warnings** **Anaphylaxis and infusion reactions:** Anaphylaxis may occur at any infusion. Patient should be premedicated with antihistamines and corticosteroids and closely monitored. **Glucose-6-phospahte dehydrogenase (G6PD) deficiency-associated hemolysis and methemoglobinemia** Screen patients at risk of G6PD deficiency prior to initiation.		course of the therapy. These may delay interpretation of ineffective pegloticase treatment and increase risk of infusion reaction.

*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>Caution/ Contraindications</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 resume 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 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 hour 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>
<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>
</td>
<td>
Common:
• Gastrointestinal
Nausea, vomiting, diarrhea

Serious:
• Hematologic
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-GP inhibitor
Increased risk of toxicity
• Statin/fibrates/ digoxin/ ciclosporin
Increased risk of myopathy and rhabdomyolysis
</td>
</tr>
</table>

*Use of colchicine to treat gout flares is not recommended in patients with renal impairment (CrCl <80 ml/min) receiving prophylactic colchicine.

Dosage modifications in hepatic impairment:

Hepatic Impairment	Gout flare treatment**	Gout flare prophylaxis
Mild to moderate	No dosage adjustment, monitor closely for AE	No dosage adjustment, monitor closely for AE
Severe	Dosage adjustment not required but may be considered; treatment course should not be repeated more frequently than every 14 days	Consider dosage adjustment

**Use of colchicine to treat gout flares is not recommended in patients with hepatic impairment receiving prophylactic colchicine.

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:

Recent or concomitant therapy	Gout flare treatment***	Gout flare prophylaxis
Potent CYP3A4 inhibitor e.g. clarithromy-cin, ketoconazo-le, itraconazole	0.5 mg at first sign of flare, followed by 0.25 mg one hour later	0.25 mg OD or every other day

<table>
<tr><td></td><td>
<table>
<tr><td>and certain protease inhibitor</td><td></td><td></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 a CYP3A4 inhibitor.
***Do not repeat courses of colchicine therapy until 3 days have elapsed.</td><td></td><td></td><td></td></tr>
<tr><td colspan="5">NSAIDs/COX-2 inhibitors</td></tr>
<tr><td>Ibuprofen</td><td>400 - 800 mg TDS
(maximum: 3200 mg daily)</td><td rowspan="6">Common:
• Gastrointestinal
GI Intolerance
• Cardiovascular
Elevated blood pressure, oedema
• Dermatological
Rash
• Hepatic
Abnormal liver function test</td><td rowspan="6">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,</td><td rowspan="6">• 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</td></tr>
<tr><td>Diclofenac</td><td>50 mg BD/TDS</td></tr>
<tr><td>Naproxen</td><td>550 - 1100 mg in 2 divided doses (275 mg tablet)
750 mg initially, then 250 mg TDS (250 mg tablet)</td></tr>
<tr><td>Meloxicam</td><td>15 mg daily</td></tr>
<tr><td>Celecoxib</td><td>400 mg stat followed by 200 mg BD subsequently</td></tr>
<tr><td>Etoricoxib</td><td>120 mg OD for 7 - 8 days</td></tr>
</table>

			perforation or ulceration • Severe hepatic or renal impairment • Severe cardiac failure	
Corticosteroids				
Prednisolone	**Flare treatment:** 30 to 40 mg/day once daily or in 2 divided doses until symptom improvement (usually 2 to 5 days), then taper gradually as tolerated (typically over 7 to 10 days). A slower taper (e.g. over 14 to 21 days) maybe required, particularly in patients with multiple recent flares. **Flare prophylaxis:** Steroid 7.5 mg prednisolone equivalent daily up to 3 to 6 months	**Common:** • **Cardiovascular** Body fluid retention, hypertension • **Dermatologic** Acne • **Gastrointestinal** GI bleeding • **Endocrine metabolic** Decreased body growth, hyperglycaemia • **Muscular skeletal** Osteoporosis • **Neurologic** Headache	**Contraindications:** • Hypersensitivity to prednisolone • Concomitant administration with live vaccines or live attenuated virus vaccines (with immunosuppress-sive doses of corticosteroids) **Caution:** • Active infections	• **CYP3A4 inhibitors (e.g. ketoconazole)** May increase serum concentration of prednisolone • **CYP3AP 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	**Common:** • **Hematologic** Bruise • **Neuromuscular and skeletal** Joint swelling	**Contraindications:** • Hypersensitivity to triamcinolone • Bleeding diastheses	• **Ciclosporin** Increase in both ciclosporin and corticosteroids

	Intra-muscular: 40 to 80 mg as a single dose; May repeat at ≥48-hour intervals if there is no flare resolution	• **Respiratory** Cough, sinusitis		activity when used concomitantly

C. TREATMENT OF GOUT IN PREGNANCY AND LACTATION

Drug	Pregnancy	Lactation
Allopurinol	Category C	Limited human data; potential toxicity
Probenecid	Category C	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
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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3. Mims Gateway. (Available at: http://www.mimsgateway.com/malaysia/overview.aspx)
4. Micromedex® Solution. (Available at: https://www.micromedexsolutions.com/)
5. Controlling gout with long term urate-lowering treatment, Managing gout in primary care Part 2, The Best Practice Advocacy Centre New Zealand (bpac^{nz}), 2021. (Available at: https://bpac.org.nz/2021/gout-part2.aspx)
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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)
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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
BCE	before common era
BMI	body mass index
BSR	British Society for Rheumatology
CHD	coronary heart disease
CI	confidence interval
CKD	chronic kidney 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
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
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
NSAIDs	nonsteroidal anti-inflammatory drugs
n-3 PUFA	omega-3 polyunsaturated fatty acids
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
SF	synovial fluid
STAT	immediately
SU	serum urate
tbsp	tablespoon
TDS	three times a day
TEAE(s)	treatment-emergent adverse event(s)
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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