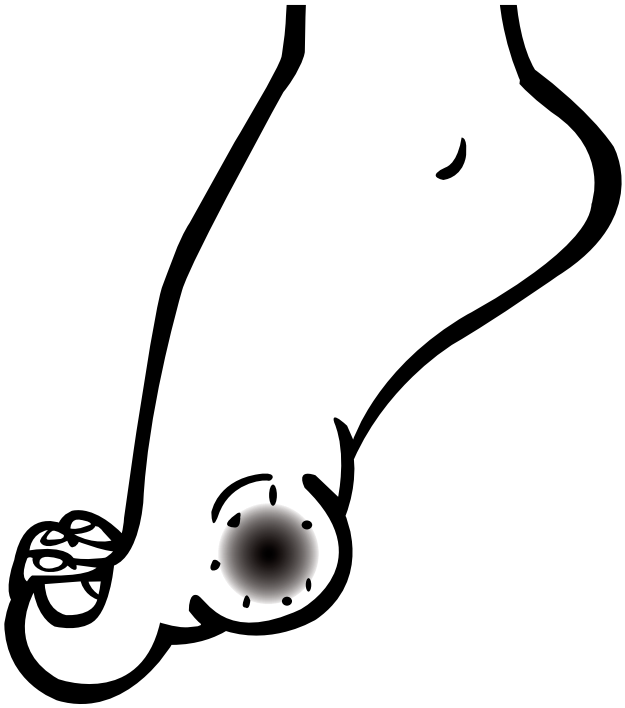
CLINICAL PRACTICE GUIDELINES

OCTOBER 2008

MOH/P/PAK/172.08 (GU)

Management of GOUT



Ministry of Health Malaysia

Malaysian Society of Rheumatology

Academy of Medicine of Malaysia

STATEMENT OF INTENT

This guideline is meant to be a guide for clinical practice, based on the best available evidence at the time of development. Adherence to this guideline may not necessarily guarantee the best outcome in every case. Every health care 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.

This guideline was issued in 2008 and will be reviewed in 2012 or sooner if new evidence becomes available

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The electronic version is available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my
http://www.msr.org.my

RATIONALE AND PROCESS OF GUIDELINE DEVELOPMENT

Rationale

The Clinical Practice Guidelines (CPG) on the Management of Gout was developed as the committee felt that gout is a common arthritis seen both in general practice and in the hospital setting. Although it is a common condition, treatment of gouty arthritis is not ideal, with many patients suffering recurrent attacks, and some going on to develop complications of the disease or its treatment. With adequate treatment using these guidelines, we hope that patients with gouty arthritis will have a better quality of life, with less pain and less complications.

This is the first Clinical Practice Guidelines on the Management of Gout. The Malaysian Society of Rheumatology, in collaboration with general physicians, family practitioners, orthopaedic surgeons, nephrologists and dieticians, were involved in preparing this guideline.

A literature search was carried out using the following electronic databases: International Health Technology Assessment websites, PUBMED, Cochrane Database of Systematic Reviews, OVID search engine and the Cochrane Controlled Trials Registry using the terms 'gout', 'crystal disease', 'gout treatment', 'gout management'. In part, we were guided by the European League of Associations of Rheumatology (EULAR) guidelines on the management of gout. All attempts were made to use local or regional data where possible. Whenever clinical recommendations were made, the best available evidence was used to support the recommendations. All efforts were made to ensure references quoted were the most current and up to date.

The committee hopes that this guideline will be useful especially to the non rheumatologists. We believe that every practitioner would be helped by using this guideline when managing simple and/or complicated gouty arthritis, bearing in mind that treatments need to be individualized for each patient depending on the clinical presentation and treatment options available locally.

The articles were graded using the modified version of the criteria used by the Catalonia Agency for Health Technology Assessment and Research (CAHTAR) Spain, while the grading of recommendation in this guideline was modified from the Scottish Intercollegiate Guidelines Network (SIGN).

The draft guideline was posted on the Ministry of Health Malaysia websites for comment and feedback. This guideline has also been presented to the Technical Advisory Committee for Clinical Practice Guidelines, and the Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

III OBJECTIVES III

The guideline is intended to provide

a. education and awareness on the proper way to diagnose, assess and investigate gout
b. evidence based guidance on the management of gout

III CLINICAL QUESTIONS III

The clinical questions to be addressed in this guideline include

1. What are the current best practices in the management of gout and its complications?
2. What is the evidence to treat asymptomatic hyperuricaemia?

III TARGET POPULATION III

This guideline is to be applied to adults above 16 years old with gout.

III TARGET GROUP III

This guideline is developed for primary care practitioners, physicians, orthopaedic surgeons, surgeons, dieticians and all health care providers involved in the management of gout.

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SUMMARY OF RECOMMENDATIONS

Lifestyle modification and dietary advice

- Lifestyle modification and dietary advice play a subsidiary role to medication to educe/prevent an acute attack of gout:

1. Achieve an ideal body mass index (BMI)	Grade C
2. Restriction or elimination of alcohol	Grade B
3. Restrict consumption of high purine foods	Grade B
4. Moderate intake of purine-rich vegetables	Grade B
5. Consumption of low fat dairy products is encouraged	Grade B
6. Adequate intake of fluid of 2-3 L daily	Grade C

Asymptomatic hyperuricaemia

- Two thirds of individuals with asymptomatic hyperuricaemia do not develop gout	Grade B
- Therefore, routine prophylactic treatment is not needed in these individuals	Grade C

Acute gouty arthritis

Acute gouty attack can be controlled by the following drugs:

1. Non-steroidal anti-inflammatory drugs (NSAIDs) Effective in relieving pain and reducing inflammation in patients with acute gout.	Grade C
2. COX-2 inhibitors In those at risk of peptic ulcer disease or intolerant of traditional NSAIDs or those requiring a prolonged course of NSAIDs treatment, COX-2 inhibitors are indicated.	Grade A
3. Colchicine An alternative drug for those whom NSAIDs and COX-2 inhibitors are contraindicated.	Grade C
4. Corticosteroids In elderly people and those with renal insufficiency, hepatic dysfunction, cardiac failure, peptic ulcer disease and hypersensitivity to NSAIDs or COX-2 inhibitors, a short course of glucocorticoids can be considered.	Grade B

Chronic gouty arthritis

Recurrent attacks of gouty arthritis, erosive gouty arthritis and chronic tophaceous gout require hypouricaemic therapy.	Grade A
1. The aim is to reduce serum urate level to <0.36mmol/L (6.0mg/dL)	Grade C
2. Hypouricaemic therapy should only be started after an acute attack is well-controlled.	Grade A
3. Once started on hypouricaemic agents, the same dose must be maintained during subsequent acute attacks.	Grade C
4. Allopurinol is effective in reducing the serum urate level.	Grade A
5. Probenecid is an alternative hypouricaemic agent if allopurinol is contraindicated.	Grade C
6. Colchicine can be used to reduce the frequency of acute attacks during the initiation of hypouricaemic therapy.	Grade A

Urate nephropathy

Increasing urine output, increasing urine pH and decreasing urate excretion are the recommended measures to treat urate nephropathy.	Grade C

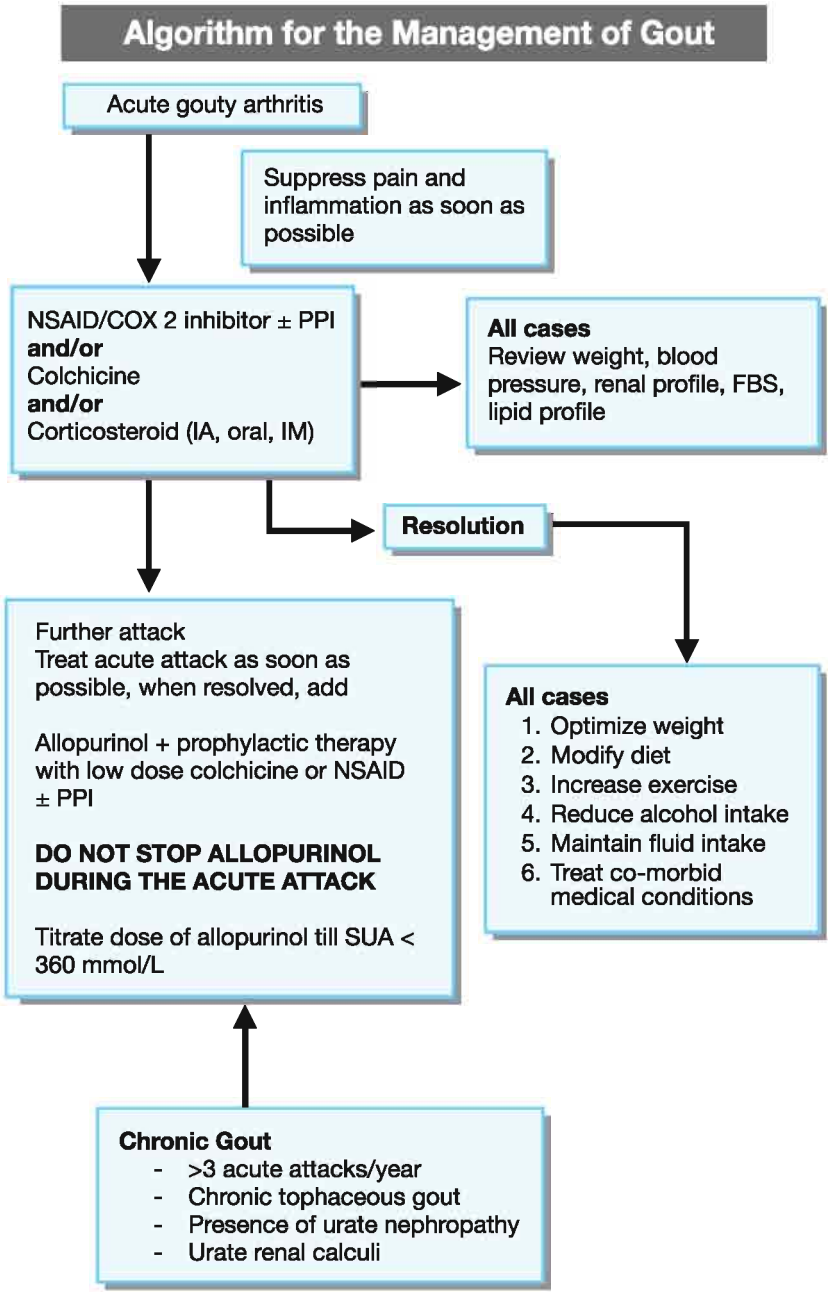
Urate nephrolithiasis

1. Extracorporeal shockwave lithotripsy and percutaneous nephrolithotomy can be used to treat intrarenal stones between 5 and 15mm or complex staghorn stones	Grade C
2. Pure urate stones are easily chemolysed using potassium citrate or sodium bicarbonate either by : a) oral ingestion b) direct irrigation	Grade B Grade C

Co-morbid conditions

Diabetes mellitus, hypertension, hyperlipidaemia and obesity are the common co-morbid conditions associated with gout and they should be screened for in individuals with asymptomatic hyperuricaemia or gout.	Grade C

Algorithm for the Management of Gout



PPI: proton pump inhibitor
IA: intra-articular
IM: intra-muscular
SUA: serum uric acid
FBS: fasting blood sugar

TOPICS

1.0 INTRODUCTION

Gout is an ancient disease as it was well described by Hippocrates in the 5th century BC.

Despite the availability of effective medications, there are many patients who still suffer from recurrent attacks of acute gout, chronic tophaceous gout and renal calculi. Some patients go on to develop renal failure.

The epidemiology of gout is now changing and this is probably due to lifestyle changes. Although there is no published data on the prevalence of gout in Malaysia, it is one of the commonest arthritis seen in general practice. The latest research suggests that the prevalence of gout is influenced by genetic factors Level 9 and associated with alcohol consumption, obesity and hypertension.

A diagnosis of gout can be established based on a history of sudden onset of a painful and swollen joint, the presence of an elevated serum urate level and/or identification of monosodium urate crystals from the affected joint.

Gout is associated with hyperuricaemia. The prevalence of hyperuricaemia varies between countries and with gender. Hyperuricaemia may develop as the result of urate overproduction, underexcretion or both.

With proper diagnosis and management, gout is a treatable condition.

2.0 CLINICAL MANIFESTATIONS OF GOUT

2.1 Gouty Arthritis

Gout progresses through several clinical phases, namely

- Acute gout
- Intercritical gout
- Chronic gout

Acute gout

Acute gout commonly presents as an acute, self-limiting, monoarticular inflammatory arthritis in approximately 90% of patients. Joints of the lower limbs are affected more often than those of the upper limbs. [2 Level 9]

The joints commonly affected are:

- 1st metatarsophalangeal joint (clinically also known as podagra)
- forefoot / instep
- ankle joint
- knee joint
- wrist joint
- elbow joint
- finger joints

Acute gout also involves extra-articular sites particularly the olecranon bursa and Achilles tendon. [2 Level 9]

On examination, there may be erythema, warmth and swelling over the involved joint, associated with extreme tenderness. Subsequently, the patient may have skin desquamation overlying the affected joint. Fever may be present.

Attacks of gout usually last from a few days to 2 – 3 weeks, with a gradual complete resolution of all inflammatory signs. [3 Level 6]

The usual course of gout is one of intermittent attacks and remissions, followed by a chronic phase. Approximately 60% of patients have a second attack within the first year, and 78% have a second attack within two years. Only 7% of patients do not have a recurrence within a 10-year period. [4 Level 9, 5 Level 9]

Intercritical gout

These are periods in between attacks when the patient is asymptomatic. [2 Level 9]

Chronic gout

Chronic gout is marked by polyarticular arthritis and the formation of tophi. [6 Level 9]

Tophi are chalky deposits of monosodium urate. They are usually subcutaneous and painless, and appear as firm, nodular or fusiform swellings. Sites of tophi include

- digits of the hands and feet (most common)
- pinna of the ear (classic albeit less common)
- bursa around elbows and knees
- Achilles tendon

Articular tophaceous gout can result in a destructive arthropathy and secondary osteoarthritis. [4 Level 9]

Tophaceous disease is more likely to occur in patients with

- polyarticular presentation
- serum urate level > 0.54 mmol/L (> 9 mg/dL)
- younger age at disease onset (i.e. 40 years or younger) [4 Level 9, 7 Level 6]

The rate of urate deposition and, consequently, the rate of tophi formation, correlate with the duration and severity of hyperuricaemia.[7 Level 6]

Gout in the Elderly

Gout in elderly patients presents differently from younger patients (Table 1).

Several areas of difference are as follows:

1. Older patients with gout are more likely to have polyarticular involvement.
2. Women make up a larger proportion of older patients with gout.
3. Gout is more likely to involve the small joints of the fingers in older patients.
4. Older patients with gout are more likely to develop tophi early in the course of their illness, often in atypical locations.
5. There is a greater association of gout with diuretic use and renal disease in older populations. [3 Level 6]

Table 1. Clinical features of gout – typical vs. elderly onset gout

Feature	Typical Gout	Elderly Onset Gout
Age of onset	Peak in mid 40s	Over 65 years
Sex distribution	Men > Women	Men = Women Over 80 years old, Women > Men
Presentation	Acute monoarthritis Lower extremity (Podagra 60%)	Polyarticular onset Upper extremity Finger involvement
Tophi	After years of attacks Elbows > Fingers	May occur early or without history of prior attacks Possibly more often over fingers
Associated features	Obesity Hyperlipidaemia Hypertension Heavy alcohol use	Renal insufficiency Diuretic use, especially in women Alcohol use less common

Polyarticular Gout

Polyarticular gout occurs more frequently in older patients.

It may mimic rheumatoid arthritis, with symmetrical small-joint involvement and tophaceous deposits on extensor tendon surfaces that resemble rheumatoid nodules. As many as 30% of patients with tophaceous gout also have low titres of rheumatoid factor, adding to the diagnostic confusion.

Postmenopausal women who are receiving diuretic therapy have a tendency to form tophi in osteoarthritis joints of the hands, mimicking inflammatory 'erosive osteoarthritis'.

Therefore, analysis of synovial fluid is essential to identify monosodium urate crystals for accurate diagnosis.

2.2 Urate Nephropathy

The incidence of gouty nephropathy in Malaysia is unknown. In the Malaysian National Renal Registry, <1% of end stage renal disease is caused by gouty nephropathy. [8] Level 6 Recent studies have suggested a strong association between gout and nephropathy, in particular kidney stone disease. [9] Level 9, [10] Level 6 After adjusting for potential confounders such as obesity and hypertension, individuals with a history of gout were 49% more likely to have a history of kidney stones. [10] Level 6

The following are 3 ways in which urate nephropathy can present: [11 Level 9, 12 Level 6, 13 Level 9]

a) Acute urate nephropathy

In this condition, urate crystals are deposited within renal tubules leading to obstruction and acute renal failure. It is often seen in patients with haematological malignancies treated with chemotherapy or irradiation. Dehydration and low urine pH are precipitating factors. Patients can present in acute renal failure.

b) Chronic urate nephropathy

In chronic urate nephropathy, urate crystals are deposited in the interstitium and in the renal medulla causing inflammation and surrounding fibrosis. This may lead to chronic irreversible renal failure. Renal impairment can occur in up to 40% of patients with chronic gout.

c) Urate nephrolithiasis (calculi)

Incidence of renal stones in patients with gout was found to be more than 10 times that of the general population.[14 Level 7] Twenty percent of patients with gout present with renal stones. These calculi present typically with flank pain, ureteric colic or haematuria. Renal calculi may be either predominantly urate (radiolucent) or a mixture of calcium oxalate and/or calcium phosphate (radio-opaque) with urate as a nidus. The incidence of urate stones accounts for 5% to 40% of all urinary calculi.[15 Level 9] Hyperuricosuria, low urinary output and acidic urine are well known contributing factors, of which the latter is the most important. Urinary alkalinization with potassium citrate or sodium bicarbonate is a highly effective treatment, resulting in dissolution of existing stones and prevention of recurrence.

3.0 DIAGNOSTIC CRITERIA FOR GOUT

Two of the following criteria are required for a clinical diagnosis:[16 Level 9]

1. Presence of a clear history of at least two attacks of painful joint swelling with complete resolution within 2 weeks.
2. A clear history or observation of podagra.
3. Presence of a tophus.
4. Rapid response to colchicine within 48 hours of starting treatment.

A definitive diagnosis can be made if crystals of monosodium urate are seen in the synovial fluid or in the tissues.

4.0 INVESTIGATIONS

4.1 Blood and Urine Tests

Investigation of gouty arthritis can be divided into 3 categories:

- **Specific investigations for confirmation of gouty arthritis**
  - Joint aspiration and crystal identification
  - Serum urate
- **To detect the presence of medical conditions associated with gout/ hyperuricaemia**
  - Blood tests as below
- **To detect complications**
  - Renal imaging
  - Skeletal x-rays

Baseline investigations

Full blood count/ differential count	To exclude infection, [17 Level 7] lympho- or myelo-proliferative disorders.
Serum creatinine/ urea	To exclude renal disease leading to hyperuricaemia or renal disease secondary to urate nephropathy or urolithiasis.[17 Level 7]
Serum urate	Upper limit of serum urate level: [18 Level 5] *Male & post-menopausal women: 0.42 mmol/L (7 mg/dL)* *Pre-menopausal women:* 0.36 mmol/L (6 mg/dL) The level of serum urate cannot be used to confirm or exclude gout. A normal serum urate level does not exclude gout. In 10% of cases, it can be normal during an attack. **Hyperuricaemia is not equivalent to gout.** [19 Level 9]
Blood glucose	To detect the presence of diabetes/insulin resistance.
Fasting lipid profile	To detect hypertriglyceridemia and low HDL cholesterol.
Urinalysis	The presence of blood and/or protein may suggest renal disorders.

Further investigations

24-hour urinary excretion	Only useful if the renal calculus is proven to urate be a urate stone. Indicated if an uricosuric agent is used.

The measurement of urinary urate excretion can be used to assess the risk of stones and to help indicate whether hyperuricaemia is due to overproduction or underexcretion of urate (range 2 – 4 mmol/24h or 0.34 – 0.67 g/24h). [20 Level 7] On a purine free diet, men with normal renal function excrete < 3.6 mmol/d (600mg/d) and if on a regular diet, they excrete < 4.2 mmol/d (800mg/d). [20 Level 9] **Most patients are underexcretors and will respond well to allopurinol.** [21 Level 9]

4.2 Joint Aspiration and Urate Crystal Identification

The only way of being certain of the diagnosis of acute gout is by identification of the monosodium urate (MSU) crystals in the synovial fluid (SF) at or around the time of an attack. Unfortunately at present, this service is not widely available.

Crystal-induced arthritis and septic arthritis occasionally coexist. The SF sample should be sent for microscopy, gram-stain, culture and crystal identification (if available) in acute arthritis.

Joint fluid characteristics: [22 Level 9, 23 Level 9]

Normal SF	Gouty Arthritis	Septic Arthritis
Very high viscosity	Low viscosity – runny	Runny
Volume low	Volume moderate/high	Volume high
Colour – straw	Straw to opalescent	Variable,Greenish/khaki
Clarity – transparent	Translucent/opaque	Opaque/purulent
Firm mucin clot	Friable	Friable
WBC/μL < 200	WBC/μL 1000 – 75,000	WBC/μL > 100,000*
< 25% PMN	> 50% PMN often	> 75% PMN
Culture	Negative	Often positive**

Note: WBC = white blood cell count/mL
PMN = polymorphonuclear leucocyte cells
* May be lower with low virulence organisms, or if partially treated
** Almost always Staphylococcus or Streptococcus

Crystal identification

MSU crystals are slender needles and/or rods, size 2 – 10 μm under plain microscopy. [23 Level 9]

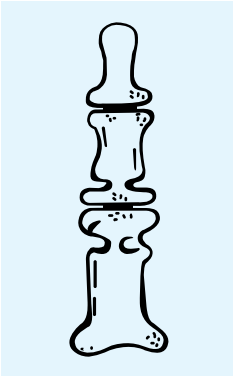
In compensated polarised light, MSU are strongly negatively birefringent. MSU crystals aligned parallel to the orienting line of the compensator are yellow; at right angles to this they appear blue. In acute gout many crystals are intracellular. They may also occasionally be seen within cells or extracellular in the interim between attacks.

Crystals can sometimes be seen with regular light microscopy, but their accurate identification is not possible without the compensated polarised light.

4.3 Skeletal X-ray

Acute gouty arthritis: Usually normal, although there may be reversible soft tissue swelling around the involved joint.

Chronic tophaceous gout: X-ray findings consist of soft-tissue abnormalities (tophi) and erosive bone lesions characterized by punched out lesions *(Figure 3).* These erosions, especially in the foot and big toe are pathognomonic, but uncommon. The joint space is usually preserved until the late stages of the disease. [24 Level 9, 25 Level 4]



Schematic illustration: Punched out erosions away from joint space which is well preserved.[26 Level 9]

Figure 3

4.4 Renal imaging

Plain abdominal x-ray detects only 10% of all urate stones.

Intravenous urogram (IVU) used to be the investigation of choice for urate stones. However, it is of limited use in patients with impaired renal function and small radiolucent pure urate stones can be difficult to demonstrate on IVU.

Ultrasonography is the investigation of choice as it would detect nephrocalcinosis, significant renal stones (>3 mm) whether radio-opaque or radiolucent, or obstructive nephropathy. However, the absence of hydronephrosis cannot firmly rule out an obstructing ureteric stone if the obstruction is so acute that it impairs renal excretion and limits any distention of the collecting system.

In this event, duplex ultrasound scan using colour Doppler to detect ureteric jets in the bladder and measurement of the renal artery resistive index can be very useful.

Unenhanced CT urogram using a spiral CT scanner is the most sensitive imaging modality to detect any stone. [27 Level 9]

MR urography offers good anatomical information on an obstruction irrespective of renal function but is poor in determining the cause of the obstruction. [28 Level 9]

Retrograde pyelography or percutaneous antegrade pyelography may sometimes be necessary.

5.0 MANAGEMENT

5.1 Lifestyle Modification and Dietary Advice

Recommended dietary and lifestyle changes include weight reduction, restriction of alcohol intake, reduced intake of purine-rich food and control of co-morbidities (e.g. hyperlipidaemia, hypertension).[29 Level 9] Dietary intervention is no longer regarded as the primary therapy but still has an important subsidiary role.

The main aim of dietary intervention is to

- achieve ideal body weight
- prevent acute attacks of gout
- reduce the serum urate level

A strict purine-free diet will reduce serum urate by only 15 – 20%. Diet is generally considered an adjunct therapy to medication.[29 Level 9]

Practical Diet Guidelines [30 Level 9, 31 Level 9]

- Maintain or achieve a healthy body weight. If weight loss is indicated, it should be gradual, 0.5 – 1.0 kg per week.

- Restriction or elimination of alcohol. [32 Level 6] Alcohol inhibits renal excretion of purines.

- Adequate fluid intake of 2 – 3L daily to keep urine dilute.

- Be aware of the purine content of foods [33 Level 6]
  (refer to Appendix 1 for detail):
  a. Restrict consumption of high purine foods i.e. red meat and seafood.
  b. Consumption of low-fat dairy products is encouraged.
  c. Moderate intake of purine-rich vegetables is not associated with an increased risk of gout.

Recommendation:

• Achieve an ideal body mass index (BMI).	(Grade C)
• Restriction or elimination of alcohol.	(Grade B)
• Restrict consumption of high purine foods.	(Grade B)
• Moderate intake of purine-rich vegetables.	(Grade B)
• Consumption of low fat dairy products.	(Grade B)
• Adequate intake of fluid of 2-3L daily.	(Grade C)

5.2 Asymptomatic Hyperuricaemia

Definition

A state in which serum urate concentration is abnormally high (male > 0.42 mmol/L (7.0 mg/dL) in males and > 0.36 mmol/L (6.0 mg/dL) in females), but neither signs nor symptoms of urate deposition have occurred.

Clinical significance

Two thirds of individuals will remain asymptomatic throughout their lives. [34 Level 6] Apart from the rare case of acute urate nephropathy, hyperuricaemia is not life threatening and readily treatable. This fact plus the absence of chronic renal failure means that in the vast majority of patients, routine prophylactic treatment is **not** required. [35 Level 9]

Hyperuricaemia is associated with three major disorders: gout, urolithiasis and nephropathy. Recently, it has been linked to the insulin resistance syndrome (metabolic syndrome, i.e. hypertension, hyperinsulinaemia, hypertriglyceridaemia, glucose intolerance).[1 Level 9, 36 Level 6, 37 Level 4] However, isolated hyperuricaemia has **not** been shown to be associated with an increased risk of death from coronary heart disease, cerebrovascular disease or all causes of death in men.[38 Level 6]

Correlation to gouty arthritis

One study followed serum urate concentration in 2046 initially healthy men for 15 years. Serum urate levels of > 0.54 mmol/L (9.0 mg/dL) were associated with a much greater incidence for gout. However, this degree of hyperuricaemia is uncommon (< 1%). [34 Level 6]

Serum urate *(mmol/L)* *(mg/dL)*	< 0.42 <7	0.42 – 0.53 7 - 8.9	> 0.53 > 9
Annual Incidence	0.1%	0.5%	4.9%

Correlation with renal stones

Increased daily urinary urate excretion is associated with a higher risk of urate and calcium oxalate stone formation, e.g. when daily urate excretion exceeds 0.65 mmol/L (11.0 mg/dL), the incidence of urolithiasis approximates 50%. [39 Level 9] This level of overexcretion is uncommon.

It has been suggested that hyperuricaemia is not of clinical importance with respect to renal disease until the serum urate level is more than twice the normal limit, 0.77 mmol/L (13 mg/dL) in men and 0.60 mmol/L (10 mg/dL) in women. [40 Level 9]

Treatment
A thorough history and examination for the causes, associated medical conditions and the presence of organ or tissue damage are required.

Contributing factors such as the use of drugs, e.g. thiazide diuretics or low-dose aspirin may be discontinued or substituted, if appropriate. Dietary purine and alcohol restriction should also be advised.

In most cases, pharmacologic treatment of asymptomatic hyperuricaemia is **not** necessary, **except** in the following conditions:

Persistent severe hyperuricaemia
Serum urate of > 0.77 mmol/L (13 mg/dL) in men and > 0.60 mmol/L (10 mg/dL) in women may be associated with some increase in nephrotoxic risk.

Persistent elevated urinary excretion of urate
Urinary excretion of urate in excess of 0.65 mmol/L/day (11mg/day) is associated with a 50% increased risk of urate calculi.

Tumour lysis syndrome
Patients about to undergo chemotherapy or radiotherapy that is likely to result in extensive tumour cytolysis may require pre-hydration and treatment with allopurinol to prevent acute urate nephropathy.

Recommendation:
- Two thirds of individuals with asymptomatic hyperuricaemia do not develop gout. (Grade B)
- Routine prophylactic treatment is not needed in asymptomatic hyperuricaemic individuals. (Grade C)

5.3 Acute Gouty Arthritis
In an acute attack of gout, effective treatment must target both the pain and the underlying inflammation. The choice of a drug depends on an assessment of its efficacy as compared with its toxicity in the individual patient. Rest and prompt treatment with full doses of non-steroidal anti-inflammatory drugs (NSAIDs) are usually the first-line treatments.

NSAIDs
Any NSAID can be used but aspirin should be avoided because it causes urate retention unless given in very high doses. Most potent NSAIDs are rapidly effective in relieving pain and reducing inflammation in patients with acute gout, particularly if the drugs are taken soon after the onset of the attack and in full therapeutic doses. [41] Level 9 Examples of NSAIDs that are used are diclofenac, indomethacin and ketoprofen. Parenteral NSAIDs can also be administered.

Caution should be exercised in those with a history of peptic ulcer disease, hypertension, renal impairment and cardiac failure. Alternative drug therapy should be considered in these patients (see below). In general, risks are greatest in elderly patients, particularly those with renal dysfunction. [42 Level 7]

Recommendation:

- NSAIDs are effective in relieving pain and reducing inflammation in patients with acute gout. (Grade C)

COX-2 Inhibitors

In those at risk of peptic ulcer disease or intolerant of traditional NSAIDs or those presenting with an acute attack of gout of several days duration, since a prolonged course of treatment is likely to be required, COX-2 inhibitors are an alternative. [43 Level 9, 44 Level 9] Studies have shown that etoricoxib, a COX-2 inhibitor, has equal efficacy to indomethacin in the treatment of acute gout, with etoricoxib showing an improved safety profile. [45 Level 1, 46 Level 1] Similar cautions as for NSAIDs should be exercised in those with renal impairment, cardiac failure, hypertension and active peptic ulcer disease.

Recommendation:

- In those at risk of peptic ulcer disease or intolerant of traditional NSAIDs or those requiring a prolonged course of NSAIDs treatment, COX-2 inhibitors are indicated. (Grade A)

Colchicine

Colchicine is an alternative drug for those whom NSAIDs and COX-2 inhibitors are contraindicated but is poorly tolerated by elderly people. [16 Level 9] Its therapeutic index is narrow and side-effects associated with colchicine treatment such as nausea, vomiting, abdominal pain and profuse diarrhoea can be so intense as to limit its usefulness. [47 Level 9] In order to reduce the risks of side effects (especially diarrhoea) it should be used in doses of 0.5mg-0.6mg bd-qds. [47 Level 9]

Caution should be exercised in those who have renal or hepatic dysfunction and in the elderly. Its toxicity can be increased with cimetidine and erythromycin. [48 Level 9]

Recommendation:

- Colchicine is an alternative drug for those whom NSAIDs and COX-2 inhibitors are contraindicated. (Grade C)

Glucocorticoids

In elderly people and those with renal insufficiency, hepatic dysfunction, cardiac failure, peptic ulcer disease and hypersensitivity to NSAIDs or COX-2 inhibitors, glucocorticoids can be considered.[42 Level 7] Intra-articular injection of glucocorticoids into the affected joint can be administered but it needs to be given by a doctor who is trained to perform such a procedure. Intramuscular injection of glucocorticoids such as triamcinolone (40-80 mg/day) or methylprednisolone (80mg/day) can be given stat. Alternatively, a short course of oral glucocorticoids can be considered. Oral prednisolone up to 0.5 mg/kg/day or its equivalent can be given and tapered off over 4 – 10 days. As the duration of treatment is usually short, side-effects due to steroids are rare.[49 Level 9] There is no role for long-term glucocorticoids in the treatment of gout. Patients should not be given repeated courses of glucocorticoids; if this is required, they should be referred for specialist opinion.

Recommendation:

- In elderly people and those with renal insufficiency, hepatic dysfunction, cardiac failure, peptic ulcer disease and hypersensitivity to NSAIDs or COX-2 inhibitors, a short course of glucocorticoids can be considered. (Grade B)

Allopurinol

Allopurinol should not be started until the acute attack has settled. **However, if the patient has been on long-term allopurinol, the drug should not be stopped during an acute attack** ***(refer to pg 14 for details).***

5.4 Chronic Gouty Arthritis

Recurrent attacks of gouty arthritis, erosive gouty arthritis and tophaceous deposits require therapy to lower serum urate levels.[50 Level 1] Other indications for the use of hypouricaemic therapy are listed in *Table 2*. The aim of hypouricaemic therapy is to prevent and reverse the consequences of urate crystal deposition in joints (gouty arthropathy), urinary tract (nephrolithiasis), renal interstitium (urate nephropathy), and tissue and parenchymal organs (tophi). The aim is to reduce the serum urate level to < 0.36 mmol/L (6.0 mg/dL).[51 Level 9]

Recommendation:

- Recurrent attacks of gouty arthritis, erosive gouty arthritis and chronic tophaceous gout require hypouricaemic therapy. (Grade A)
- The aim is to reduce serum urate level to <0.36mmol/L (6.0mg/dL). (Grade A)

Hypouricaemic therapy should only be started after an acute attack is well-controlled (about two weeks after the attack).[50 Level 1] This is because hypouricaemic therapy started during an attack may prolong the attack or lead to rebound flares. For the same reason, hypouricaemic drugs should not be stopped or adjusted during an acute attack. *Table 3* shows the important points that should be discussed with the patients.

Table 2. Indications for hypouricaemic drugs

1.	Frequent and disabling attacks of gouty arthritis (3 or more attacks/year).
2.	Clinical or radiographic signs of erosive gouty arthritis.
3.	The presence of tophaceous deposits.
4.	Urate nephropathy.
5.	Urate nephrolithiasis.
6.	Impending cytotoxic chemotherapy or radiotherapy for lymphoma or leukaemia.

Table 3. Important points at the initiation of hypouricaemic drugs

1.	NSAIDs/COX-2 inhibitors and colchicine do not lower serum urate.
2.	Hypouricaemic drugs have no analgesic or anti-inflammatory effect.
3.	Once treatment with a hypouricaemic agent has been initiated, it should not be stopped during an attack.
4.	There may be more frequent attacks of acute gouty arthritis at the initiation of therapy, especially in the first three months. Prophylaxis with NSAIDs/COX-2 inhibitors or colchicine can be used to reduce the frequency of acute attacks.
5.	Hypouricaemic therapy is a life-long treatment.
6.	Life style modification is an important adjunctive therapy.

Recommendation:

- Hypouricaemic therapy should only be started after an acute attack is well-controlled. (Grade A)
- Once started on hypouricaemic agents, the same dose must be maintained during subsequent acute attacks. (Grade C)

Allopurinol

Allopurinol, one of the most commonly available hypouricaemic drugs in Malaysia, is a xanthine oxidase inhibitor. Its hypouricaemic effect is superior than probenecid. [52 Level 3] It is primarily excreted by the kidneys and therefore the dose of allopurinol must be adjusted for patients with renal impairment [53 Level 9] *(refer to Appendix 2)*. In patients with normal renal function, start at 100 – 150mg once daily, increasing by 100 – 150mg steps every 4 weeks to a dose of 300mg once daily. In patients who require higher doses, an assessment by a specialist is recommended. The aim is to reduce the serum urate level to < 0.36 mmol/L (6.0 mg/dL)[51 Level 9] and maintain it at that level with the minimum dose of allopurinol. During initiation of allopurinol therapy, colchicine (1 – 2 tablets per day) can be used to reduce the frequency of acute attacks. [54 Level 3] Colchicine prophylaxis can be continued until the patient is free of acute attacks for six months or target serum urate level is

achieved for one month. For patients who cannot tolerate colchicine, low dose NSAIDs or COX-2 inhibitors can be used.

The indication for starting allopurinol must be clear, **as severe life-threatening complications can occur.** Adverse effects include rash, bone marrow suppression, aplastic anaemia, agranulocytosis, granulomatous hepatitis and jaundice. Life threatening hypersensitivity syndrome[55 Level 9] which consists of fever, rashes, hepatitis, eosinophilia and renal impairment has been well documented. Allopurinol desensitization can be used to desensitize an individual who has had a mild non-life threatening rash on taking allopurinol.[56 Level 8]

Allopurinol has important interactions with several medications:

1. Higher incidence of rash in combination with ampicillin.
2. Higher incidence of bone marrow suppression with cyclophosphamide.
3. Increases toxicity of azathioprine and mercaptopurine, and therefore the dose of these drugs should be reduced to about one third.
4. Prolongs the half-life of warfarin and theophylline.

Recommendation:

- Colchicine can be used to reduce the frequency of acute attacks during the initiation of hypouricaemic therapy. (Grade A)
- Allopurinol is effective to reduce serum urate level. (Grade A)

Probenecid

Probenecid is a uricosuric agent. It can be used as an alternative to allopurinol in patients with normal renal function. It is contraindicated in patients with uric acid overproduction and overexcretion (24 hours urinary urate excretion of more than 800mg per day) or in those with urate nephropathy or nephrolithiasis because of the risk of crystal precipitation and stone formation.[57 Level 9] Renal function and 24 hours urinary urate excretion must be assessed before commencement of probenecid. Initial doses of 0.5 to 1gm are given and may be increased to 1.5 to 2gm in divided doses. [57 Level 9] The side effects of probenecid are gastrointestinal disturbance and a hypersensitive rash; serious side effects are rare.

Probenecid interacts with following drugs:

1. Decreases tubular excretion of salicylate, penicillin.
2. Increases the serum frusemide concentration and augments its diuretic effect.

Recommendation:

- Probenecid is an alternative hypouricaemic agent if allopurinol is contraindicated. (Grade C)

Urate Nephropathy

The following measures are suggested in patients with urate nephropathy:[12 Level 6 ,13 Level 9]

Increase urine output

Three litres of water per day is recommended to achieve a urine output of greater than 2½ litres per day. More may be required if there is excessive insensible and gastrointestinal loss. However, in end stage renal failure, fluid intake should be limited.

Increase urine pH

This helps to prevent urate stone formation and promotes dissolution of stones. The target urine pH is 6.5 – 7.

Preparations available

a. Potassium salt: Potassium citrate – initial dose 40 – 50 mmol/day (maximum 100 mmol/day)
b. Sodium salt: e.g. sodium bicarbonate can be used BUT the added sodium may increase sodium urate formation which can serve as a nidus for calcium oxalate precipitation at a higher pH.

Decrease urate excretion

This can be done by restricting dietary purine intake or taking allopurinol.

Recommendation:

- Increase urine output, increase urine pH and decrease urate excretion are the recommended measures to treat urate nephropathy. (Grade C)

Urate Nephrolithiasis

In general, intrarenal stones less than 5 mm in size can be observed unless they are causing pain. Intrarenal stones between 5 and 15 mm or complex staghorn stones need referral to a urologist for further management such as extracorporeal shockwave lithotripsy (ESWL) or percutaneous nephrolithotomy (PCNL). Ureteric stones are managed conservatively if they are uncomplicated (minimal associated obstruction, no sepsis) and of a size < 5mm and/or at a location (lower ureter) deemed likely to pass spontaneously. However, if a stone fails to pass after 2 weeks, referral for removal is advisable.

Pure urate stones are easily chemolysed using potassium citrate or sodium bicarbonate, either by means of oral ingestion[58 Level 6] or direct irrigation.[59 Level 9] Long-term chemoprophylaxis using potassium citrate has been shown to be highly effective.[60 Level 6]

Recommendation:

- Extracorporeal shockwave lithotripsy and percutaneous nephrolithotomy can be used to treat intrarenal stones between 5 and 15mm or complex staghorn stones. (Grade C)
- Pure urate stones are easily chemolysed using potassium citrate or sodium bicarbonate either by
  a) oral ingestion. (Grade B)
  b) direct irrigation. (Grade C)

Surgical Management of Gout

In general, surgical intervention is the last resort for the treatment of gouty arthritis.

In the chronic tophaceous gout, surgical options are considered in the following conditions:

- Advanced tophi deposition resulting in major joint destruction.
- Loss of involved joint movements associated with severe pain.
- Tophi collection causing pressure symptoms, e.g. carpal tunnel compression at the wrist.
- Tophaceous ulcer.
- Cosmetic, e.g. ear lobe tophi.

Ulceration overlying tophi collection at the great toe may require debridement, depending on the state of the ulcer and/or if there is secondary infection. Debridement may need to be repeated and frequent dressings required. Sodium bicarbonate solution has been advocated for the dressing of such ulcers with tophi collection.

6.0 MEDICAL CONDITIONS ASSOCIATED WITH ASYMPTOMATIC HYPERURICAEMIA/ GOUT

The following medical conditions are associated with asymptomatic hyperuricaemia/gout: [2] **Level 9**

1. Obesity
2. Hypertension
3. Hyperlipidaemia, particularly hypertriglyceridaemia (type IV lipoproteinaemia)
4. Impaired glucose tolerance/diabetes mellitus

Therefore these conditions must be screened for and treated accordingly in all the patients with asymptomatic hyperuricaemia or gout, as they can lead to atherosclerotic vascular disease if not treated early.

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Appendix 1

Low purine content	Moderate purine content (9 – 100mg purines/ 100gm food)	High purine content (100 – 1000mg purines/ 100gm food)
Bread & crackers	Red meat	Brains
Butter/margarine (use in moderation)*	Fish (except those in high list)	Liver
Cake & cookies*	Poultry (chicken, duck)	Kidney
Carbonated beverages	Shellfish (prawns, crabs, mussels, cockles, etc)	Sweet bread (spleen)
Cereal & cereal products	Asparagus	Heart
Milk & dairy products	Cauliflower	Goose
Chocolate & ice cream*	Spinach	Anchovies (ikan bilis)
Fruits & fruits juices	Mushrooms	Sardines
Eggs	Green peas	Mackerel (ikan kembung)
Gelatin desserts	Dried peas/beans/lentils	Herring
Nuts		Scallops
Sugars, syrups, sweets		Meat extracts (e.g. Bovril)
Vegetables (except those in moderate list)		Yeast (taken as supplement)
White sauce & vinegar		
Rice, noodles, pasta		
Oils & fats*		
Salt		
Herbs		
Beverages – tea, coffee, soda		

* Recommended in moderation due to fat content

Appendix 2

Allopurinol dose adjustment based on renal function

Creatinine clearance (mL/min)	Allopurinol dose
0	100mg every 3 days
10	100mg every 2 days
20	100mg daily
40	150mg daily
60	200mg daily
80	250mg daily
100	300mg daily

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LEVELS OF EVIDENCE SCALE

Level	Strength of Evidence	Study Design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4	Good to Fair	Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled historical trial
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case report anecdotes

SOURCES : ADAPTED FROM THE CATALONIAN AGENCY FOR HEALTH TECHNOLOGY ASSESSMENT & RESEARCH. (CAHTAR) SPAIN

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and/or clinical experiences of respected authorities: indicates absence of directly applicable clinical studies of good quality

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