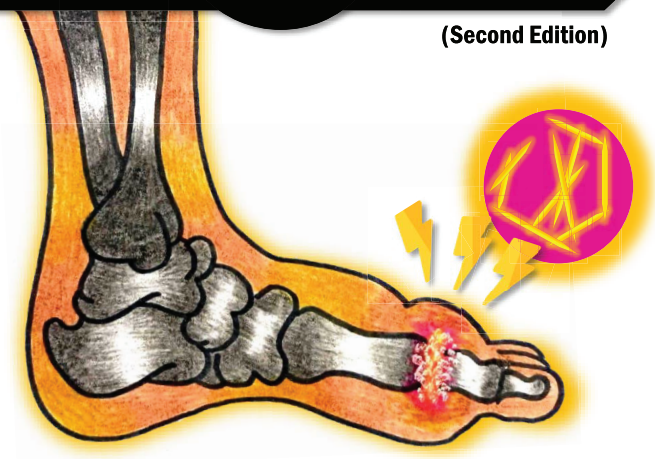
QUICK REFERENCE FOR
HEALTH CARE PROVIDERS

MANAGEMENT OF GOUT

(Second Edition)



Ministry of Health Malaysia

Malaysian Society of Rheumatology

Academy of Medicine Malaysia

KEY MESSAGES

1. Gout is a disease caused by monosodium urate (MSU) crystal deposition with any of the following clinical presentations (current or prior): gout flare, chronic gouty arthritis, or subcutaneous tophus.
2. Not all hyperuricaemic individuals develop MSU crystal deposition or gout. There is insufficient evidence to recommend urate-lowering therapy (ULT) to treat asymptomatic hyperuricaemia.
3. Modifiable risk factors for gout include obesity/overweight, alcohol, high-fructose corn syrup, red meat, seafood [except n-3 polyunsaturated fatty acid (PUFA)-rich fish] & medications especially diuretics.
4. Gout can be prevented by adopting a healthy lifestyle which includes maintenance of a healthy body weight, avoidance of alcohol & adherence to Dietary Approaches to Stop Hypertension (DASH) diet. Diuretics should be replaced by an alternative drug, if possible, when used as an antihypertensive agent to reduce the risk of gout.
5. Screening for comorbidities associated with gout e.g. hypertension, diabetes mellitus, hyperlipidaemia, coronary heart disease & renal disease including urolithiasis should be done upon diagnosis & during follow-up.
6. The ACR-EULAR 2015 Classification Criteria (refer to http://goutclassificationcalculator.auckland.ac.nz or https://www.mdcalc.com/acr-eular-gout-classification-criteria) can be used to diagnose gout based on clinical features & serum urate (SU). A score of ≥8 classifies a patient as having gout.
7. Treat-to-target (T2T) strategy aiming for SU <360 µmol/L should be applied in the treatment of all gout patients including those with chronic kidney disease (CKD).
8. For ULT, allopurinol is the first-line therapy (*start low, go slow*). When allopurinol is contraindicated or not tolerated, febuxostat or uricosuric agents can be considered.
9. Gout flare should be treated promptly & adequately with colchicine, nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitors or corticosteroids. The choice of drug is guided by patient's concomitant comorbidities.
10. Prophylaxis for gout flares should be used for at least 3 - 6 months when initiating ULT. The preferred choices are stepwise dose increase of ULT and/or concomitant colchicine.

This Quick Reference provides key messages & a summary of the main recommendations in the Clinical Practice Guidelines (CPG) Management of Gout (Second Edition)

Details of the evidence supporting these recommendations can be found in the above CPG, available on the following websites:

Ministry of Health Malaysia: www.moh.gov.my

Academy of Medicine Malaysia: www.acadmed.org.my

Malaysian Society of Rheumatology: https://msr.my

CLINICAL PRACTICE GUIDELINES SECRETARIAT

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Presint 1,
Federal Government Administrative Centre 62590
Putrajaya, Malaysia
Tel: 603-88831229
E-mail: htamalaysia@moh.gov.my

DIAGNOSIS

- Diagnosis of gout should not be made based on hyperuricaemia alone.
- The cut-off SU level to diagnose hyperuricaemia based on urate saturation threshold is a SU concentration of >6.8 mg/dL (408 μmol/L) at physiological pH and body temperature.
- 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 2 weeks or more after complete resolution of flare.

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

DIFFERENTIAL DIAGNOSES

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

The main differential diagnoses of gout are:

i. septic arthritis (key differential diagnosis)
ii. acute calcium pyrophosphate crystal arthritis
iii. psoriatic arthritis
iv. reactive arthritis

ASYMPTOMATIC HYPERURICAEMIA

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

TREAT-TO-TARGET

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

NON-PHARMACOLOGICAL TREATMENT

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

PHARMACOLOGICAL TREATMENT

- Established indications for initiation of ULT for gout patients are:
  - recurrent gout flares (≥2 flares in 12 months) **OR**
  - presence of ≥1 tophi **OR**
  - presence of radiographic damage attributable to gout

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

- T2T should also be applied in the treatment of gout patients with concomitant CKD.

MONITORING

<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</td><td rowspan="2">Every 4 weeks during dose titration & then every 6 months when dose is stable</td><td rowspan="2">Every 4 weeks during dose titration & then every 6 months when dose is stable</td><td rowspan="2">Every 4 weeks during dose titration & then every 6 months when dose is stable</td><td>Annually</td><td rowspan="2">Every 3 months</td></tr>
<tr><td>Liver function test</td><td>Every 4 weeks for first 6 months & then every 3 months</td></tr>
<tr><td>SU and renal profile</td><td colspan="5">Every 4 weeks until SU <360 µmol/L then every 6 months</td></tr>
<tr><td>Fasting blood sugar, Fasting serum lipid Haemoglobin A1c (HbA1c)</td><td colspan="5">At least annually</td></tr>
<tr><td>Full and microscopic examination of urine (Urine FEME)</td><td colspan="5">During clinical review
(urine protein to creatinine ratio or albumin to creatinine ratio if there is concurrent hypertension/diabetes mellitus)</td></tr>
<tr><td>Plain radiography of affected joints</td><td colspan="5" rowspan="2">Repeat when indicated</td></tr>
<tr><td>Ultrasonography of kidney ureter & bladder</td></tr>
<tr><td>Electrocardiogram Echocardiogram (ECHO)</td><td colspan="5">When clinically indicated</td></tr>
</table>

REFERRAL

- Referral of gout patients to a rheumatologist may be considered for the following:
  - diagnostic indications
    - unclear diagnosis with atypical clinical presentations including suspected gout in
      - women with onset before menopause
      - men with early onset at age <30 years without predisposing risk factors for gout
  - therapeutic indications
    - refractory to conventional therapy despite drug adherence
      - gout flare that fails to resolve despite treatment as recommended by the CPG
      - recurrent flares although SU target of <360 µmol/L is achieved
      - failure to achieve SU target of <360 µmol/L after a trial of at least 3 months of allopurinol at a maximally tolerated dose
      - tophaceous gout with progressive joint damage, active symptoms or growing tophi despite medical treatment
    - complicated gout with destructive joint changes
    - hypersensitivity or intolerance to allopurinol
  - special group indication
    - gout in pregnancy
- Surgical management of tophi may be considered when there is:
  - uncontrolled infection
  - entrapment neuropathy
  - risk of permanent joint damage
- Gout with urolithiasis should be assessed by a urologist.

PHARMACOLOGICAL TREATMENT FOR GOUT
A. URATE-LOWERING THERAPY

<table>
<tr><th>Drug</th><th>Recommended dose</th><th>Possible AEs</th></tr>
<tr><td>Allopurinol</td><td>Initial: 100 mg/day, increase 100 mg every 2 - 4 weeks until target is achieved
Maximum: 900 mg/day

Dosage modifications in renal impairment:<table><tr><th>Estimated Glomerular Filtration Rate (ml/min/1.73m^2)</th><th>Initial dose</th></tr><tr><td>>60</td><td>100 mg daily</td></tr><tr><td>30 - 60</td><td>50 mg daily</td></tr><tr><td><30</td><td>50 mg every other day</td></tr></table></td><td>Common:
• Maculopapular rash, pruritus
• Nausea, vomiting
Serious:
• Stevens-Johnson syndrome (SJS), Toxic Epidermal Necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS)
• Transaminitis, cholestasis
• Bone marrow suppression</td></tr>
<tr><td>Probenecid</td><td>Initial: 250 mg BD for 1 week; may increase to 500 mg BD
Maximum:1000 mg BD (increase dosage in 500 mg increment every 4 weeks)

Renal impairment of CrCl <30 ml/min: Avoid use</td><td>Common:
• Rash
• Nausea, vomiting
Serious:
• SJS
• Aplastic anaemia, leukopenia, thrombocytopenia, neutropenia
• Hepatic necrosis
• Anaphylaxis, hypersensitivity reaction</td></tr>
<tr><td>Febuxostat</td><td>Initial: 40 mg OD; if SU level is >6.0 mg/dL (360 µmol/L) after 2 - 4 weeks, 80 mg OD may be considered

Dosage modifications in renal impairment:<table><tr><th>CrCl (ml/min)</th><th>Dose</th></tr><tr><td>≥30</td><td>No adjustment</td></tr><tr><td>15-29</td><td>Maximum dose 40 mg OD</td></tr></table></td><td>Common:
• Rash
• Diarrhoea, nausea
• Liver function abnormalities
Black Box Warning
Cardiovascular:
• Higher rate of CV death in gout patients with established CV disease</td></tr>
</table>

B. TREATMENT OF FLARE & FLARE PROPHYLAXIS

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

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

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

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

Dosage modifications in renal impairment:
<table>
<tr><th>CrCl (ml/min)</th><th>Gout flare treatment*</th><th>Gout flare prophylaxis</th></tr>
<tr><td>>60 - 89</td><td>No dosage adjustment, monitor closely for AE</td><td>No dosage adjustment, monitor closely for AE</td></tr>
<tr><td>30 - 60</td><td>No dosage adjustment, monitor closely for AE</td><td>Limit dose to 0.5 mg daily</td></tr>
<tr><td><30, renal replacement therapy</td><td>Consider alternative therapy</td><td>Consider alternative therapy</td></tr>
</table>
*Use of colchicine to treat gout flares is not recommended in patients with renal impairment (CrCl <80 ml/min) already receiving prophylactic colchicine.
</td><td>
Common:
Nausea, vomiting, diarrhoea

Serious:
Myelosuppression
Neuromuscular disease, neuromyotoxicity
</td></tr>
<tr><td>Ibuprofen</td><td>400 - 800 mg TDS
(maximum: 3200 mg/day)</td><td rowspan="6">Common:
• Gastrointestinal Intolerance
• Elevated blood pressure, oedema
• Rash
• Abnormal liver function test</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>Maximum 15 mg/day</td></tr>
<tr><td>Celecoxib</td><td>400 mg stat followed by 200 mg BD subsequently</td></tr>
<tr><td>Etoricoxib</td><td>Maximum 120 mg/day</td></tr>
</table>

ALGORITHM ON MANAGEMENT OF GOUT

Acute monoarthritis/oligoarthritis

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

Clinical features of gout

1. Involvement of the first metatarsophalangeal joint, ankle or midfoot
2. Redness, extreme pain and loss of function in the affected joint
3. Time to maximal pain <24 hours and complete resolution of symptoms within 14 days
4. Recurrence of typical attacks increase the likelihood of diagnosis
5. Clinical evidence of tophus (present in chronic gouty arthritis)

- 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/oligoarthritis - manage accordingly

Yes → **Diagnosis of gout**

Investigations

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

Treatment of gout flare

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

***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

No → Continue to monitor for possible indications in future