Gouty arthritis: diagnosis and treatment updates

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ABSTRACT
Gout is a common medical condition, and gouty arthritis is almost a daily case for the rheumatologist. Gout passes through asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and chronic tophaceous gout, each stage managed differently. Diagnostic and therapeutic modalities will be discussed.

Key words: gout, hyperuricemia, colchicine, allopurinol, febuxostat.

Abbreviations: ULT-urate lowering therapy; NSAID-nonsteroidal antiinflammatory drug; COX-2-cyclooxygenase 2; GI-gastrointestinal; IL-1-interleukin-1; ACTH-adrenocorticotropic hormone; AHS-allopurinol hypersensitivity reaction; XOI-xanthine oxidase inhibitor; CKD-chronic kidney disease.

1. INTRODUCTION
Hyperuricemia is a common condition (Al-Arfaj et al. 2001). Gout (mono-sodium urate crystals deposition disease) is a common condition with prevalence in United States of 3.9% (Zhu et al. 2011). There are some risk factors associated with higher prevalence of hyperuricemia and gout (MIAO et al. 2008), and a number of pharmacological agents can induce hyperuricaemia, and sometimes gout. (Scott et al. 1991). New modalities are being used to diagnose gouty arthritis such as ultrasound, CT-scan and MRI (Ruiz et al. 2009). Gout passes through stages, asymptomatic hyperuricemia then clinical phases (acute/recurrent gout, intercritical gout, and chronic tophaceous gout) and each stage managed in a different way (Zhang et al. 2006).

2. DISCUSSION
Hyperuricemia is a common condition in our country, in a study conducted in the central area of Saudi Arabia in which consumption of sea food is less and as alcohol is prohibited in our religion, 8.4% found to be hyperuricemic taking the cut-off value of normal uricemia 360Mmol/L (6mg/dL) (Al-Arfaj et al. 2001). Racial differences in hyperuricemia exists as in a study in the US general population, hyperuricemia prevalence was 21.2% (Zhu et al. 2011). Our concern about asymptomatic hyperuricemia is the context of our article is the risk of development of acute gouty arthritis, it was found that With prior serum urate levels of 9 mg/dl or more, the annual incidence rate of gouty arthritis was 4.9 percent, compared with 0.5 percent for urate levels of 7.0 to 8.9 mg/dl and 0.1 percent for urate levels below 7.0 mg/dl and so conservative management of asymptomatic hyperuricemia is the choice rather than urate lowering therapy (ULT), (Campion et al. 1987).
There are some risk factors associated with higher prevalence of hyperuricemia and gout, increase of daily consumption of meat and seafood, alcohol, overweight or obesity, hypertension, abnormal triglycerides (MIAO et al. 2008). And impaired renal function as uric acid clearance significantly reduced in gout (Gibson et al. 1980).

A number of pharmacological agents can induce hyperuricemia, and sometimes gout, Alcohol, diuretics, salicylates, pyrazinamide, ethambutol, nicotinic acid, cyclosporin, 2-ethylamino-1,3,4-thiadiazole, fructose and cytotoxic agents (Scott et al. 1991). Aspirin in low doses (75–150 mg/day) has significant effects on the plasma urate, and should be used as required for cardiovascular prophylaxis. However, aspirin in analgesic doses (600–2400 mg/day) interferes with uric acid excretion and should be avoided (Jordan et al. 2007).

Estrogen plays a key role in protecting women from hyperuricemia and gout as it may enhance renal uric acid excretion. Menopause was associated with higher serum uric acid levels (McClylory et al. 2009). Gout (mono-sodium urate crystals deposition disease) is a common condition with a prevalence in United States of 3.9% (Zhu et al. 2011).

Gout passes through stages, asymptomatic hyperuricemia as we discussed earlier, then clinical phases (acute/recurrent gout, intercritical gout, and chronic tophaceous gout), (Zhang et al. 2006). In acute gouty arthritis, A single joint is involved in about 85% to 90% of first attacks, with the first metatarsophalangeal joint being the most commonly affected site. The initial attack is polyarticular in 3% to 14%. Acute gout is predominantly a disease of the lower extremities, but eventually, any joint of any extremity may be involved. Ninety percent of patients experience acute attacks in the great toe at some time during the course of their disease. Next in order of frequency are the insteps, ankles, heels, knees, wrists, fingers, and elbows. Acute attacks rarely affect the shoulders, hips, spine, sacroiliac joints, sternoclavicular joints, acromioclavicular joints, or temporomandibular joints (Parhami et al. 1993; Musgrave et al. 2000). Gout can present in a number of ways, although the most usual is a recurrent attack of acute inflammatory arthritis (a red, tender, hot, swollen joint) (Chen et al. 2008).

There are few helpful old and evolving diagnostic modalities. We will start with the value of testing serum uric acid during acute gouty arthritis attack as it can be normal, so normal uric acid level at presentation does not exclude an acute gouty attack (Schlesinger et al. 2009). Synovial fluid analysis under polarized light microscopy, demonstration of mono-sodium urate crystals (Figure 1), they have a needle-like morphology and strong negative birefringence (Schlesinger et al. 2007). We have the old imaging modality which is x-rays, but new modalities are being used to diagnose gouty arthritis such as ultrasound, CT-scan and MRI, the findings of each one will be briefly mentioned here (Ruiz et al. 2009). x-rays in patients with the very first manifestations of gout, no radiographic findings are present but for an increase in the soft tissues. Typical plain radiographic features of chronic gout include visualization of tophi as soft-tissue or intraosseous masses, and the presence of a nondecolorizing erosive arthropathy with erosions that are well defined with sclerotic or overhanging margins (Figure 2). In ultrasound the most useful elemental lesion is the double-contour sign – a hyperechoic, irregular band over the superficial margin of the joint cartilage, produced by deposition of mono-sodium urate crystals on the surface of the hyaline cartilage (Figure 3). Dual-energy CT has the potential to allow noninvasive diagnosis of gout, and also measurement of total body urate burden (Figure 4). MRI allows early detection of tophi and bone erosion in patients with gout. Synovial involvement may also be appropriately evaluated with MRI. The relative lack of specificity of MRI and the technique’s high cost, however, limit its role in routine clinical assessment of gout (Figure 5).

The detailed part of our discussion comes here to our daily practice of gout treatment,

I) Acute Gout Attack: (Khanna et al. 2012)

Algorithm 1: Overview of management of an acute gout attack. ULT urate-lowering therapy; NSAID nonsteroidal antiinflammatory drug; COX-2 cyclooxygenase 2; GI gastrointestinal; IL-1 interleukin-1.

Adapted from Arthritis Care & Research. 2012, 64 (10): 1431–1446

Note the following as well:

In Acute gouty arthritis the affected joints should be rested and analgesic, anti-inflammatory drug therapy commenced immediately, and continued for 1–2 weeks (Jordan et al. 2007). Topical ice application to be an appropriate adjunctive measure to 1 or more pharmacologic therapies for acute gouty arthritis

- NSAIDs: no consensus to preferentially recommend any one specific NSAID as first-line treatment.
- Colchicine: for gout attacks where the onset was no greater than 36 hours prior to treatment initiation.

Loading dose of 1.2 mg of colchicine followed by 0.6 mg 1 hour later and this regimen can then be followed by gout attack prophylaxis dosing 0.6 mg once or twice daily. If the patient receiving prophylactic colchicines within 14 days prior to the attack, consider alternative agent NSAID or steroid.

- Systemic and intraarticular corticosteroids and adrenocorticotropic hormone (ACTH): intraarticular corticosteroids for acute gout of 1 or 2 large joints, Where intraarticular joint injection is impractical, oral corticosteroids, prednisone, or prednisolone at a starting dosage of at least 0.5 mg/kg per day for 5–10 days, followed by discontinuation or alternately, 2–5 days at the full dose, followed by tapering for 7–10 days, and then discontinuation. Consider ACTH for patients unable to take oral anti-inflammatory medications.
- Interleukin-1 (IL-1) inhibitor (anakinra 100 mg subcutaneously daily for 3 consecutive days or canakinumab 150 mg subcutaneously as an option for severe attacks of acute gouty arthritis refractory to other agents. Patient unable to take orally: intravenous or intramuscular
methylprednisolone at an initial dose at 0.5–2.0 mg/kg, subcutaneous synthetic ACTH at an initial dose of 25–40 IU, with repeat doses as clinically indicated (for either ACTH or intravenous steroid regimens).

**Management of an Acute Gout Attack**

**General Principles:**
- Acute gouty arthritis attacks should be treated with pharmacologic therapy
- To provide optimal care, pharmacologic treatment should be initiated within 24 hours of acute gout attack onset
- Ongoing pharmacologic ULT should not be interrupted during an acute gout attack

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**Assess severity**
- | Mild-Moderate Pain, Particularly For an Attack Affecting Only 1 or a Few Small Joints, or 1-2 Large Joints |
- | Severe Pain, Particularly For a Polyarticular Attack or an Attack Affecting Multiple Large Joints |

**Monotherapy**
- NSAID (\(^{\text{a}}\) or COX-2 inhibitor)
- Systemic Corticosteroids

**Treatment regime**
- Supplement with Topical Ice as needed

**Inadequate Response**
- Consider alternative diagnosis
- Switch to alternate monotherapy
- Option: Add-on combination therapy Table 1

**Successful Outcome**
- Treatment Outcome
- Off-Label Therapies in Development

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\(^{\text{a}}\) Evidence Grades for Recommendations:
- **Level A**: Supported by multiple (i.e., more than one) randomized clinical trials or meta-analyses
- **Level B**: Derived from a single randomized trial, or nonrandomized studies.
- **Level C**: Consensus opinion of experts, case studies, or standard-of-care.

\(^{\text{b}}\) Colchicine was recommended as an appropriate option for acute gout if started within 36 hours of symptom onset.

\(^{\text{c}}\) Selective COX-2 inhibition with agents available outside the USA such as etoricoxib (Evidence A) was recommended as an option in patients with G1 contra-indications or intolerance to NSAIDs, but selective COX-2 inhibition shares many adverse events with NSAID therapy. COX-2 inhibition therapy with celecoxib (Evidence B) requires high doses and has unclear risk-benefit ratio at this time.

\(^{\text{d}}\) Inadequate response is defined as

- \(< 20\% \) improvement in pain score within 24 hours or
- \(< 50\% \) at \( \geq 24 \) hours

\( > \) Off-label use of biologic IL-1 inhibitor treatment has been investigated for acute gout when non-biologic therapeutic categories are ineffective or contra-indicated, but this approach is not approved for gout by medical regulatory agencies at the time this is written.
II) prophylaxis of attacks of acute gout: (Khanna et al. 2012)

![Algorithm 2: prophylaxis of acute gout.](image)

**Initiate Prophylaxis:**
- With, or just prior to initiating ULT
- Medication choices
  - Low dose Colchicine: Low dose colchicine, 0.6 mg once or twice daily
  - First line: OR (Outside US, 0.5 mg once or twice a day)
  - Low dose NSAIDs: with proton pump inhibitor (where indicated)
  - e.g. Naproxen 250 mg twice daily

*Second line: Low dose Prednisone or Prednisolone* (≤10 mg/day)
(if colchicine and NSAIDs both are not tolerated, contra-indicated, or ineffective)

Evaluate gout symptoms while on ULT
- Activity of gout signs/symptoms
- No signs/symptoms

Continue pharmacologic anti-inflammatory prophylaxis

**DURATION:** Treatment for the greater of:
- At least 6 months
- 3 months after achieving target serum urate appropriate for the patient (No tophi detected on physical exam)
- 6 months after achieving target serum urate appropriate for the patient (One or more tophi detected on physical exam)

^Without specific task force panel (TFP) vote, the TFP advised that this measure requires particular, continued attention to risk-benefit ratio

5 Examples include: acute gouty arthritis in the past 3 months, presence of palpable tophus or tophi, chronic tophaceous gouty arthropathy (with chronic synovitis) in the past 3 months

*Lack of consensus: Prednisone/prednisolone at doses above 10 mg/day.

* The TFP did not specifically address case scenarios involving renal impairment adjusted colchicine dosing for gout attack prophylaxis

# Evidence Grades for Recommendations:
**Level A:** Supported by multiple (i.e. more than one) randomized clinical trials or meta-analyses
**Level B:** Derived from a single randomized trial, or nonrandomized studies.
**Level C:** Consensus opinion of experts, case studies, or standard-of-care.

Algorithm 2: prophylaxis of acute gout.

Adapted from - Arthritis Care & Research. 2012, 64 (10): 1447–1461

Urate lowering therapy: (Khanna et al. 2012)

nonpharmacologic ULT measures in gout:
lifestyle choices for optimal management of life-threatening comorbidities in gout patients, including coronary artery disease and obesity, metabolic syndrome, diabetes mellitus, hyperlipidemia, and hypertension. Dietary recommendations to limit consumption of purine-rich meat and seafood as well as high fructose corn syrup–sweetened soft drinks and energy drinks and reduce consumption of alcohol (particularly beer, but also wine and spirits) and avoidance of alcohol overuse in all gout patients and encourage the consumption of low-fat or nonfat dairy products and vegetable intake in gout patients.

Pharmacologic ULT, to achieve the serum urate target < 6 mg/dl: in any patient with established diagnosis of gouty arthritis and any of the following: tophus/tophi detected clinically or radiologically, 2 or more attacks of gouty arthritis per year, chronic kidney disease CKD stage 2 or worse and past urolithiasis. Commencement of ULT should be delayed until 1–2 weeks after inflammation has settled (Jordan et al. 2007). ULT is indefinite and regular monitoring of serum urate (every 2–5 weeks) during ULT titration, including continuing measurements once the serum urate target is achieved every 6 months.

- XOI xanthine oxidase inhibitor (allopurinol or Febuxostat) are First line drugs. Upward dose titration of XOI to respective maximum appropriate dose. Febuxostat can be substituted for allopurinol or vice versa in the event of drug intolerance and adverse events
- uricosuric agent (e.g., probenecid, fenofibrate, or losartan) added to XOI drug or vice versa contra-indicated in gout patients with a creatinine clearance <50 ml/minute, History of urolithiasis and Elevated urine uric acid
- Pegloticase is appropriate for patients with severe gout disease burden and refactoriness to, or intolerance of, conventional and appropriately dosed ULT. Pegloticase 8 mg every 2 weeks and no consensus yet about duration.

And finally we’ll have a brief outlines of commonly used drugs for treatment of gout in our country namely Colchicine, Allopurinol and Febuxostat.

1- Colchicine

Class/ Mechanism of action:
Blocks the processing of IL-1β (Martinon et al. 2006) and inhibits E-selectin–mediated adhesiveness to neutrophils (Ryckman et al. 2004).

Indications & Dosing in gout:
Loading dose of 1.2 mg of colchicine followed by 0.6 mg 1 hour later and this regimen can then be followed by gout attack prophylaxis dosing 0.6 mg once or twice daily. (KHANNA et al. 2012)

Renal impairment (Curiel et al. 2012):
Used with caution in all patients with advanced renal insufficiency

Acute gout flare:
Severe CKD: not more than once every 2 weeks, give alternate therapy.
Dialysis: a single 0.6-mg dose, and should not be repeated more than once every 2 weeks.

Prophylaxis:
Severe CKD: 0.3 mg/d
Dialysis: 0.3 mg twice a week.

Side Effects:
Gastrointestinal side effects: increased peristalsis, cramping abdominal pain, diarrhea, nausea, and vomiting (Donahue et al. 2001), neuromyopathy (Kunck et al. 1987) and Pancytopenia (Hung et al. 2005).

Pregnancy:
Colchicine has no negative effect on fertility and pregnancy (Diav-Citrin et al. 2010).

Drug interactions:
Rhabdomyolysis may also occur in these settings and is more common in individuals who are also taking a statin (HMG-CoA reductase inhibitor) or cyclosporine (Chattopadhyay et al. 2001). Fatal interactions between clarithromycin and colchicine in patients with renal insufficiency (Curiel et al. 2012).

Contraindications:
Use of colchicine with P-gp inhibitors (eg, cyclosporine, tacrolimus, amiodarone, quinidine, azole antifungals, some calcium channel blockers, vinca alkyloids, erythromycin, etc. (Yu DK et al. 1999) or strong CYP3A4 inhibitors (eg, protease inhibitors, macrolide antibiotics, azole antifungals, etc. (http://medicine.iupui.edu/clinpharm/ddis/ClinicalTable.asp. 2010))
2- Allopurinol (for gout treatment)
Class/ Mechanism of action: xanthine oxidase inhibitor (Becker et al. 2005)

Dose: (KHANNA et al. 2012)
Starting dosage should be no greater than 100 mg/day for any patient, and start at 50 mg/day in stage 4 or worse CKD
HLA–B*5801 testing should be considered in select patient subpopulations at an elevated risk for allopurinol hypersensitivity reaction (AHS).
Those with HLA–B*5801 and of Korean descent with stage 3 or worse CKD or of Han Chinese or Thai extraction irrespective of renal function.

Renal dose (Curiel et al. 2012):
Should be used with caution (and may be contraindicated) in renal impairment.
50-100 mg daily and increased by 50-100 mg every 2 to 4 weeks if required.
Creatinine clearance is between 10 and 20 mL/min, 200 mg/d
Creatinine clearance is 10 mL/min, should not exceed 100 mg/d
Creatinine clearance is 3 mL/min, the interval between doses may need to be lengthened (eg, 300 mg twice a week or less)

Side Effects:
Common side effects include gastrointestinal intolerance and skin rashes (Fam et al. 2001). Other adverse reactions include fever, toxic epidermal necrolysis, alopecia, bone marrow suppression with leukopenia or thrombocytopenia, agranulocytosis, aplastic anemia, granulomatous hepatitis, jaundice, sarcoid-like reaction, and vasculitis. The most severe reaction is the allopurinol hypersensitivity syndrome, which may include fever, skin rash, eosinophilia, hepatitis, progressive renal insufficiency, and death (Hande et al. 1984; Singer et al. 1986).
Aplastic anemia, pure red cell aplasia, and pancytopenia have also been observed in patients with CKD (Curiel et al. 2012).

Drug interactions:
Potentiation of the immunosuppressive and cytolytic effects of 6-mercaptopurine and azathioprine, which are metabolized in part by xanthine oxidase (Ragab et al. 1974)

3- Febuxostat
Class/ Mechanism of action: xanthine oxidase inhibitor (Becker et al. 2005).

Dose:
40 mg and 80 mg daily, 120mg per day can be given (Avena-Woods et al. 2010)
Renal dose: 80mg once-daily, safe and well tolerated in different renal function groups, requiring no dose adjustments necessary based on differences in renal function in individuals. Creatinine clearance below 30 mL/min: not been studied. (Curiel et al. 2012)

Side Effects:
liver function test abnormalities, nausea, arthralgia, and rash Periodic monitoring of liver function, principally hepatic transaminase enzyme levels, is suggested by the manufacturer of febuxostat. (www.uloric.com. 2009)

Drug interactions:
Decreased metabolism of azathioprine and mercaptopurine is an expected result of administration of a xanthine oxidase inhibitor, and a need for continued use of any of these three drugs is considered by the manufacturer to be a contraindication to the use of febuxostat (www.uloric.com. 2009).

3. CONCLUSION
Gouty arthritis is a common and fortunately treatable disease with evolvement of many diagnostic and therapeutic modalities to save our patient from developing chronic gouty arthritis.

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REFERENCES
Figure 1
Figure 2
Radiography of the foot in a dorsal–plantar projection showing extensive bone erosions involving the first and fifth metatarsal phalangeal joints, and proximal and distal interphalangeal joints. Typical intratophus calcifications may be seen in intraosseous tophi and in periarticular tophi (Adapted from Arthritis Research & Therapy 2009, 11:232.).
Figure 3
Ultrasonography patterns indicating the presence of gout. Double contour sign: transversal ultrasound imaging of the knee joint in the anterior intercondile area. The double contour image is shown as an anechoic line paralleling bony contour femoral cartilage (Adapted from Arthritis Research & Therapy 2009, 11:232).

Figure 4
Computed tomography images demonstrating extensive tophaceous deposits. Three-dimensional volume-rendered computed tomography images of the right foot from a patient with chronic gout, demonstrating extensive tophaceous deposits (visualized as red) – particularly at the first metatarsal phalangeal joint, midfoot and Achilles tendon (Ref: Adapted from Arthritis Research & Therapy 2009, 11:232).
Figure 5
T2-weighted magnetic resonance imaging scans. Coronal gradient echo T2-weighted magnetic resonance imaging (MRI): two nodular images with an intermediate signal (tophi) under the external collateral ligament and inside the posterior cruciate ligament of the knee. An external meniscus tear may be seen close to urate deposition (Ref: Adapted from Arthritis Research & Therapy 2009, 11:232)