Pearls and Pitfalls in Gout Management

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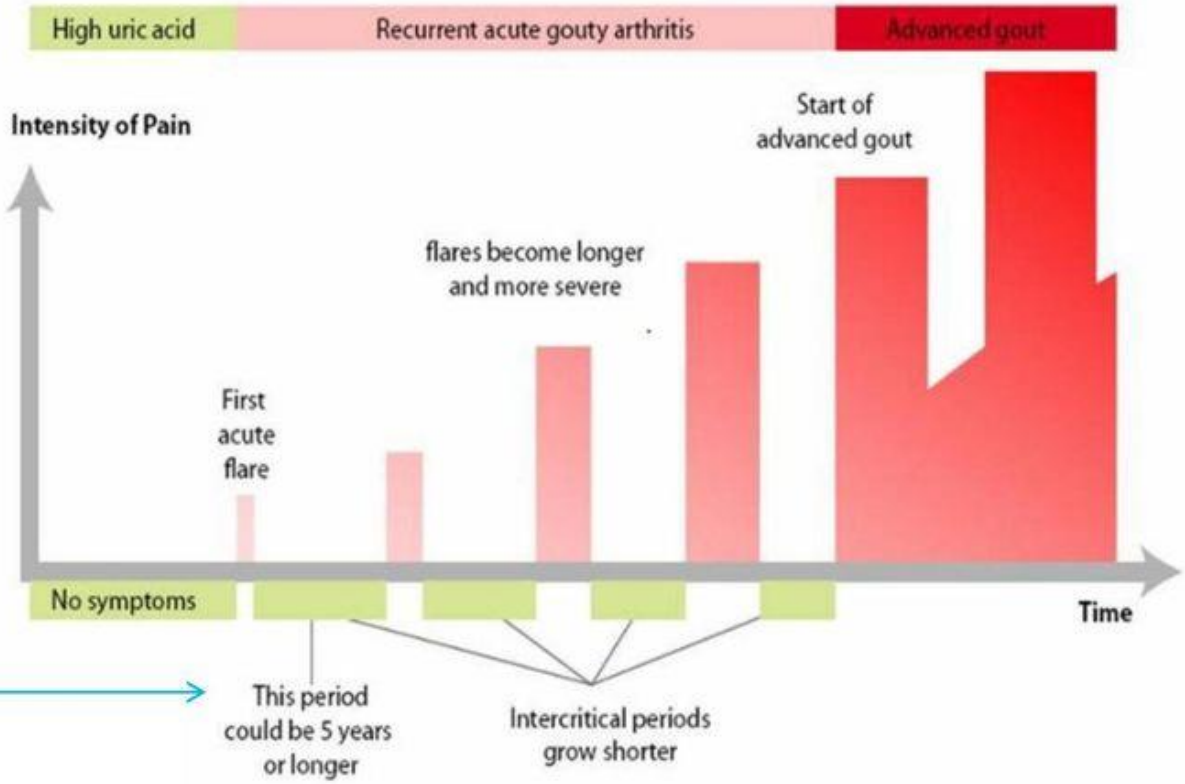
#1 Gout is not always a monoarthritis

The classic FIRST gout flare

- Intense pain, redness, swelling
- Maximal severity reached in 12 – 24 hours
- Autoresolution in a few days to weeks even if untreated
- 80% are monoarticular (1st MTP 50% > knee > other lower extremity joint > upper extremity joint
- Redness often extend past the joint (can mimic cellulitis or dactylitis)
- Resolution can be accompanied by desquamation

Natural history of gout



- ~ 1 yr: 62%
- 1 ~ 2 yr: 16%
- 2 ~ 5 yr: 11%
- 5 yr ~ : 13%

Asymptomatic hyperuricemia → Asymptomatic MSU deposits → Intermittent flares → Chronic gout

Curr Opin Rheumatol 2014;26:181-91
Primer on the Rheumatic Diseases. 12th ed.

Gout flare in “established gout”

- Often polyarticular
- Any joint can be affected
  - Even axial joints
- Can also affect soft tissue (bursitis, tenosynovitis…)
- Episode onset and resolution often less “defined”

Treatment of acute gout

Recommended first-line options:		
	Dose	Contra-indications
Colchicine **Best if used within 12 hours of flare onset**	Loading dose of 1.2 mg followed 1 hour later by 0.6 mg on day 1 then 0.6 mg BID	• Severe renal impairment • Patients receiving strong CYP3A4 inhibitors such as cyclosporine or clarithromycin
NSAIDS +/- PPI	Depends on the agent	• Renal impairment • Cardiovascular disease • Peptic ulcer disease
Corticosteroids	Oral • 30–35 mg/d of prednisone equivalent for 3–5 days or • 15-20 mg/d of prednisone equivalent with tapering over 10-14 days Intra-articular	

#2 Lifestyle modifications are important, but usually not sufficient to treat gout.

Risk factors for hyperuricemia and gout (may not not be causal)

Nonmodifiable risk factors	Modifiable risk factors
Age	Obesity
Gender	Hypertension
Ethnicity	Hyperlipidemia
Genetic variants	Cardiovascular disease
	Diabetes mellitus
	Chronic kidney disease
	Dietary factors
	Alcohol
	Medications altering urate balance

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All patients with gout should be investigated for metabolic syndrome

Specific Recommendations:
GENERAL HEALTH, DIET, AND LIFESTYLE MEASURES FOR GOUT PATIENTS#:

Evidence Grades for Recommendations:
Level A: Supported by multiple (ie, 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.

ACR 2012

- **Weight loss for obese patients, to achieve BMI that promotes general health**
- **Healthy overall diet ^**
- **Exercise (Achieve physical fitness)**
- **Smoking cessation**
- **Stay well hydrated**

C

Avoid	Limit	Encourage >
• Organ meats high in purine content (eg, sweetbreads, liver, kidney) B	Serving Sizes of: • Beef, Lamb, Pork • Seafood with high purine content (eg, sardines, shellfish) B	• Low-fat or non-fat dairy products B
• High fructose corn syrup-sweetened sodas, other beverages, or foods C	• Servings of naturally sweet fruit juices • Table sugar, and sweetened beverages and desserts • Table salt, including in sauces and gravies C	• Vegetables C
• Alcohol overuse (defined as more than 2 servings per day for a male and 1 serving per day for a female) in all gout patients B • Any alcohol use in gout during periods of frequent gout attacks, or advanced gout under poor control C	• Alcohol (particularly beer, but also wine and spirits) in all gout patients B	

^Without a specific task force panel (TFP) vote, adherence to diets for cardiac health and control of co-morbidities such as obesity, metabolic syndrome, diabetes, hyperlipidemia, and hypertension was stressed for gout patients, as appropriate.

> The TFP recommendation to "encourage" intake was not intended to advocate excesses in consumption of specific dietary items. There was a lack of TFP voting consensus on: Cherries and Cherry Products, Ascorbate (In Supplements or Foods), Nuts, Legumes. The TFP did not specifically vote on the question of limits on consumption of purine-rich vegetables and legumes.

Food and beverages that affect the risk of hyperuricemia and gout

Increase risk	Decrease risk	Neutral risk
Alcohol: Beer > Spirit > Wine Fructose Red meat Organ meat Seafood	Vitamin C Low-fat dairy products	Vegetables rich in purines: peas, beans, spinach, mushrooms Overall protein intake

Fructose and Gout

"Sugar should be reduced to a minimum. The sweeter fruits should not be taken."

– Osler, 1893

- Fructose induces uric acid formation by the same mechanism as alcohol
- In order of risk increase: Sugar-sweetened soft drink, fruit juice, fructose rich fruits (apples and oranges)

HOWEVER…

Lowering the serum urate by more than 50 µmol/L is not possible by diet alone

#3 Almost everyone with gout needs a urate-lowering therapy

EULAR 2016

- ULT should be considered and discussed with every patient with a definite diagnosis of gout from the first presentation.
- ULT is indicated in all patients with
  - Recurrent flares
  - Tophi
  - Urate arthropathy and/or renal stones
- Initiation of ULT is recommended close to the time of first diagnosis in patients
  - Presenting at a young age
  - Very high SUA level (480 mmol/L)
  - Comorbidities (renal impairment, hypertension, ischaemic heart disease, heart failure)

ULT – 3 classes

- Drugs that inhibit urate production (xanthine oxidase inhibitors)
  - Allopurinol
  - Febuxostat
- Drugs that normalise renal urate excretion (uricosurics)
  - Probenecid
  - Benzbromarone
  - Lesinurad
- Drugs that catalyse the conversion of urate to the more water soluble and readily excretable allantoin (recombinant uricases)
  - Pegloticase
  - Rasburicase (used for tumor lysis syndrome)

Commonly used ULT's:

- Allopurinol
- Allopurinol
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- Allopurinol
- Febuxostat

Allopurinol

- No “maximum” dose; should be titrated upward monthly until uric acid target reached
  - The classic 300 mg dose is insufficient for a large proportion of the population
- Normal kidney function: Start 100 mg/d and increase by 100 mg increments monthly
- Renal impairment: Start at 50 mg/d and increase by 50 mg increments monthly
- Target: 360 micromol/L if no tophi; 300 micromol/L if tophi

Allopurinol

Table 3. Core recommendations in the use of allopurinol and uricosuric ULT in gout*

Allopurinol
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 (evidence B)
Gradually titrate maintenance dose upward every 2–5 weeks to appropriate maximum dose in order to treat to chosen SUA target (evidence C)
Dose can be raised above 300 mg daily, even with renal impairment, as long as it is accompanied by adequate patient education and monitoring for drug toxicity (e.g., pruritis, rash, elevated hepatic transaminases; evidence B)
Prior to initiation, consider HLA–B*5801 in selected patients, specifically in subpopulations at higher risk for severe allopurinol hypersensitivity reaction (e.g., Koreans with stage 3 or worse CKD, and Han Chinese and Thai irrespective of renal function; evidence A)

ACR 2012

Febuxostat (Uloric)

- 40 – 80 mg/day
- Cost 10X more than allopurinol
- Side effects
  - GI upset
  - Liver function test abnormalities
- Black box warning – Cardiovascular death
- Indication: Intolerance or contra-indication to allopurinol

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

William B. White, M.D., Kenneth G. Saag, M.D., Michael A. Becker, M.D., Jeffrey S. Borer, M.D., Philip B. Gorelick, M.D., Andrew Whelton, M.D., Barbara Hunt, M.S., Majin Castillo, M.D., and Lhanoo Gunawardhana, M.D., Ph.D., for the CARES Investigators*

Table 1. CARES Study Results

N (%)	Uloric (N=3,098)	Allopurinol (N=3,092)	Hazard Ratio (95% CI)
Composite Primary Endpoint:	335 (10.8)	321 (10.4)	1.03 (0.89, 1.21)
Cardiovascular death	134 (4.3)	100 (3.2)	1.34 (1.03, 1.73)
Nonfatal myocardial infarction	111 (3.6)	118 (3.8)	0.93 (0.72, 1.21)
Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73, 1.41)
Unstable angina with urgent coronary revascularization	49 (1.6)	56 (1.8)	0.86 (0.59, 1.26)
Additional Endpoint:			
All-cause mortality	243 (7.8)	199 (6.4)	1.22 (1.01, 1.47)

Other low potency ULT

- Losartan
- Calcium channel blockers?
- Fenofibrate
- Atorvastatin

- **Thiazide diuretics elevate serum urate levels

#4 You can (and probably should) start urate-lowering therapy during an acute gout attack

Not REALLY evidence based…

Finally, the task force did not give specific guidance on whether urate-lowering drugs should be initiated during a flare or whether a traditional 2 weeks delay from flare termination should be observed. Two small trials have suggested that allopurinol initiation during an acute gout attack did not prolong the duration of flares nor worsen its severity as compared with delayed initiation.

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But…

- In the clinic, we do it all the time.
- Expert opinion suggest that the likelihood of a patient ever being started on ULT is higher if started during an attack

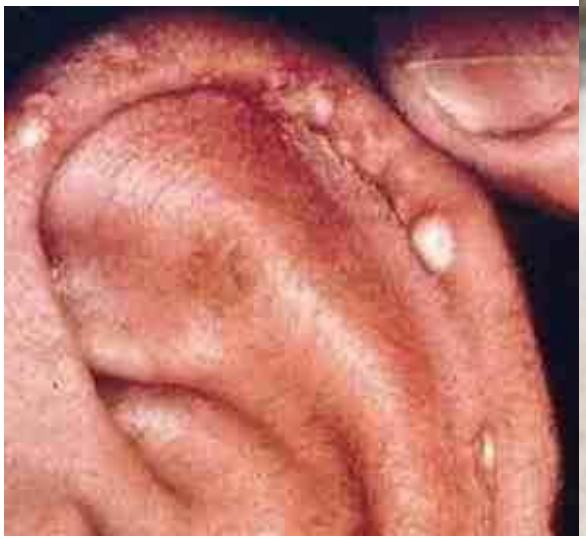
#5 You should always start a prophylaxis against acute attacks when initiating urate-lowering therapy

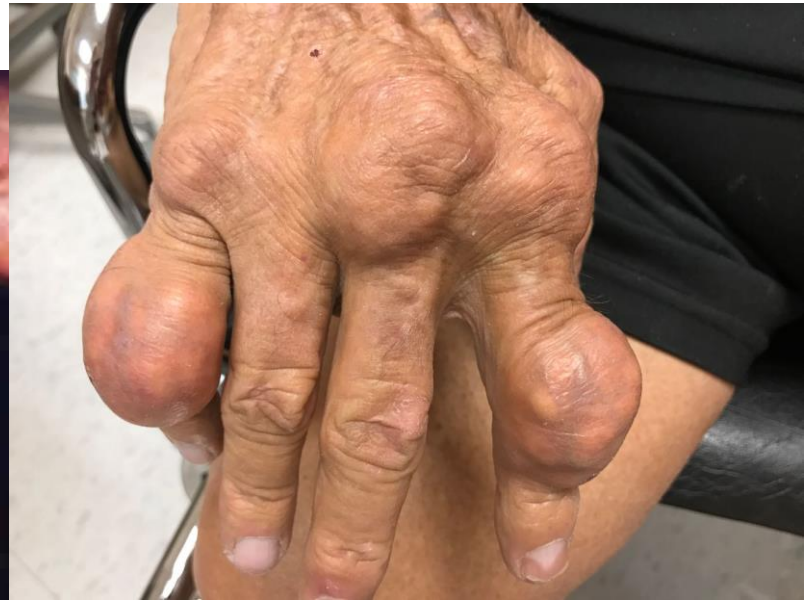
Prophylaxis choices

- Colchicine, 0.6 mg/d (reduce to 0.3 mg/d if renal impairment)
- Low dose NSAIDS
- Low dose prednisone (< 7.5 mg/day - if NSAIDS and colchicine contra-indicated)

For how long?

- No tophi: 3 – 6 months after uric acid target reached and stable
- Tophi: 6 months after resolution of tophi
  - Can take years…





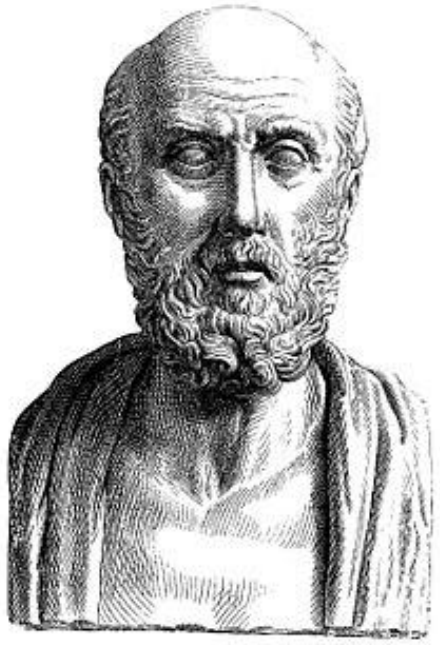
If a patient develop a flare-up during initiation of ULT, don’t stop the ULT; simply treat the flare-up +/- adjust prophylaxis

Bonus key points!

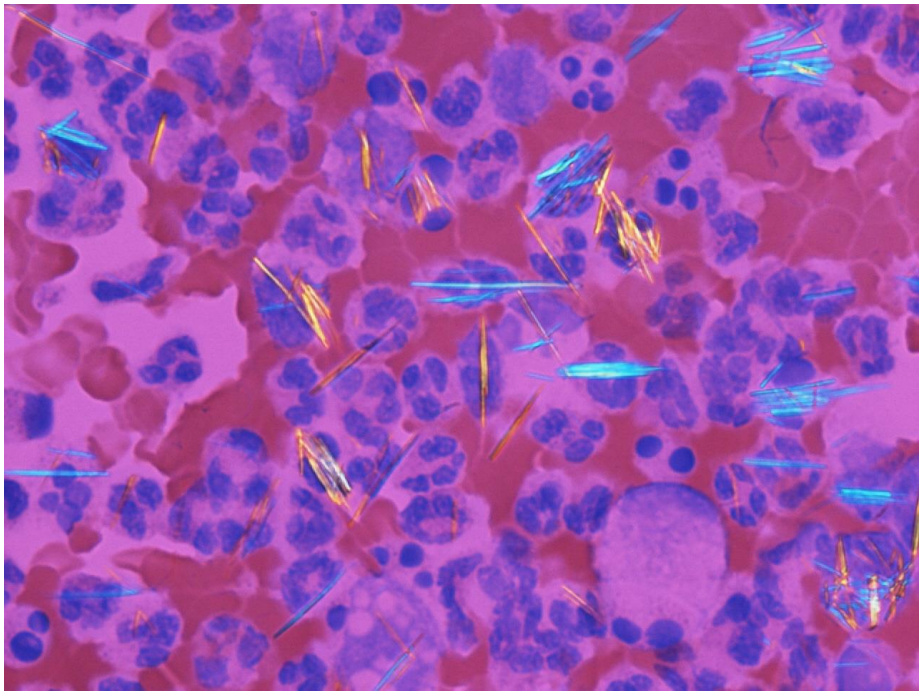
Premenopausal women don't have gout

"A women do not take the gout, unless her menses be stopped"

- Hippocrates 1886



EXTRACELLULAR urate crystals are not pathognomonic of acute gout



Gout increases the risk of joint infection, and vice versa

A normal uric acid level do not rule out an acute gout attack

Coffee consumption reduces the risk of gout