GOUT AND RISK MANAGEMENT

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DISCLOSURES

- None

OBJECTIVES

1. Discuss gout risk factors and diagnosis.
2. Understand gout management strategies individualized to the person: A simultaneous three- pronged approach: urate lowering therapy, anti-inflammatories and risk mitigation.
3. Recognize that gout is a chronic condition with chronic cardiovascular and renal complications affecting mortality.

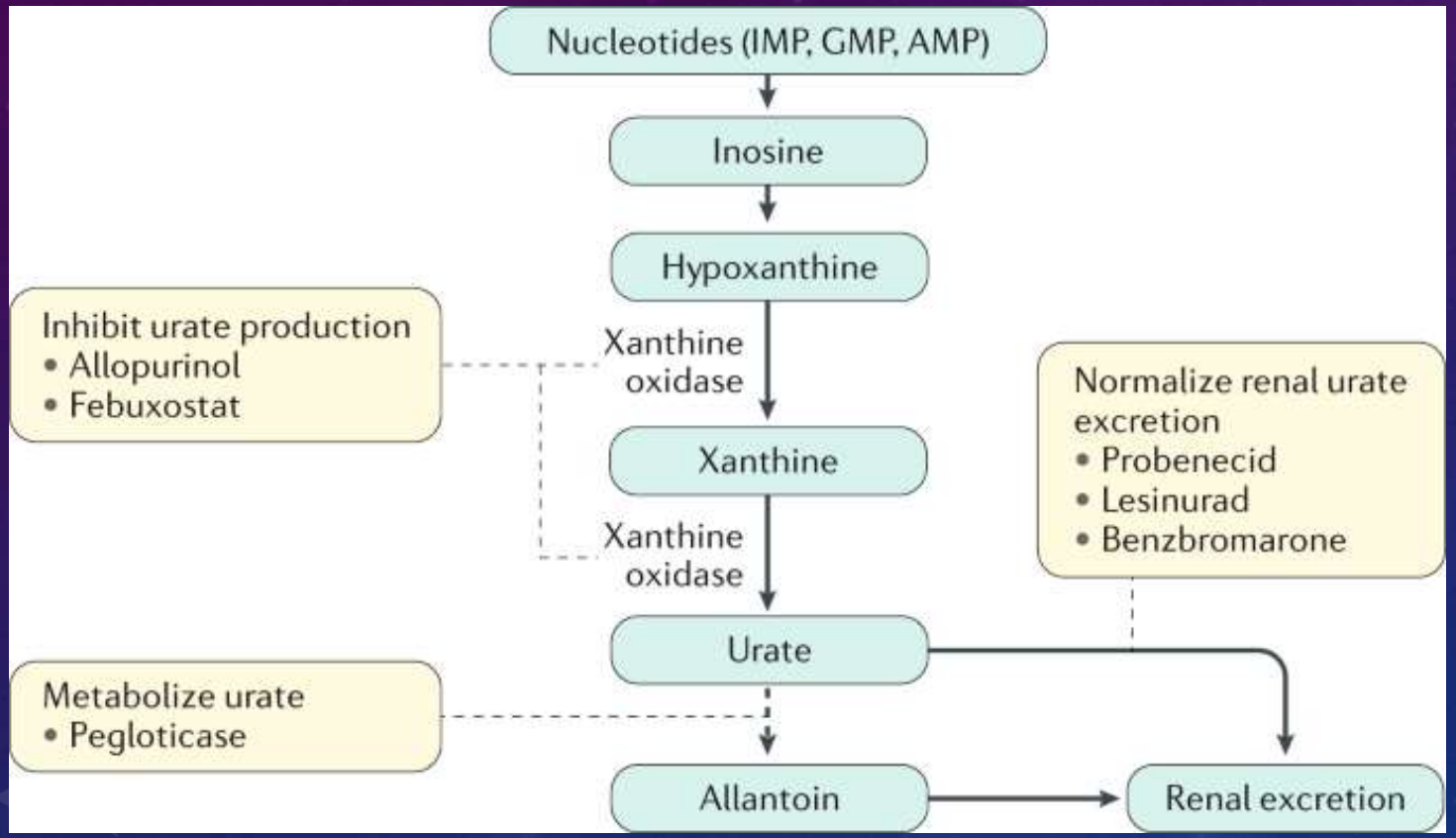
EPIDEMIOLOGY OF GOUT

- Most common inflammatory arthritis in US
- Most common cause of inflammatory arthritis in men age > 40.
- Not common in premenopausal women unless risk actors (e.g. CKD). Estrogen is uricosuric.
- Prevalence of gout may have increased by 50% over last couple decades due to increasing rates of metabolic syndrome, obesity.
- Hyperuricemia in 20% American population. But of those w/ hyperuricemia, 15-20% develop gout.

RISK FACTORS FOR GOUT

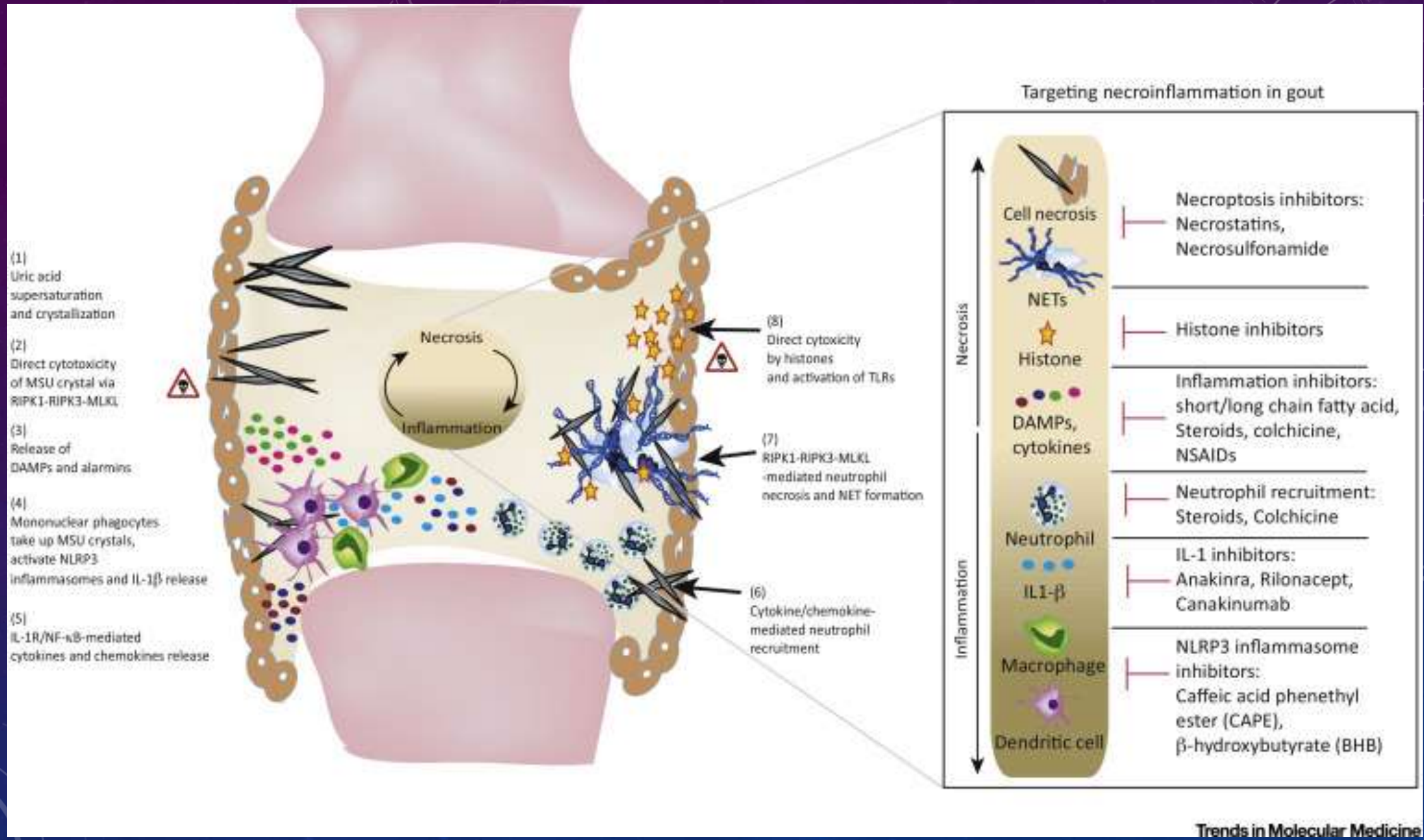
- Male sex
- Older age
- Hypertension
- Obesity
- Metabolic Syndrome
- Renal Insufficiency
- Alcoholism
- Family history gout
- High purine diet
- Diuretics, Low dose Aspirin
- High Cell Turnover States – malignancies, Psoriasis

GOUT PATHOPHYSIOLOGY



- Humans/Apes missing active Uricase enzyme which is otherwise found in most mammals.
- **Underexcretion of uric acid (UA) (80-90%)**
- Overproduction of UA
- Combination
- Not required, but can obtain 24 hr Urine UA, creatinine to determine if overproduction vs underexcretion
  UA > 800mg/24 hrs = Overproduction

Dalbeth, N., Choi, H.K., Joosten, L.A.B. *et al.* Gout. *Nat Rev Dis Primers* **5,** 69 (2019). https://doi.org/10.1038/s41572-019-0115-y



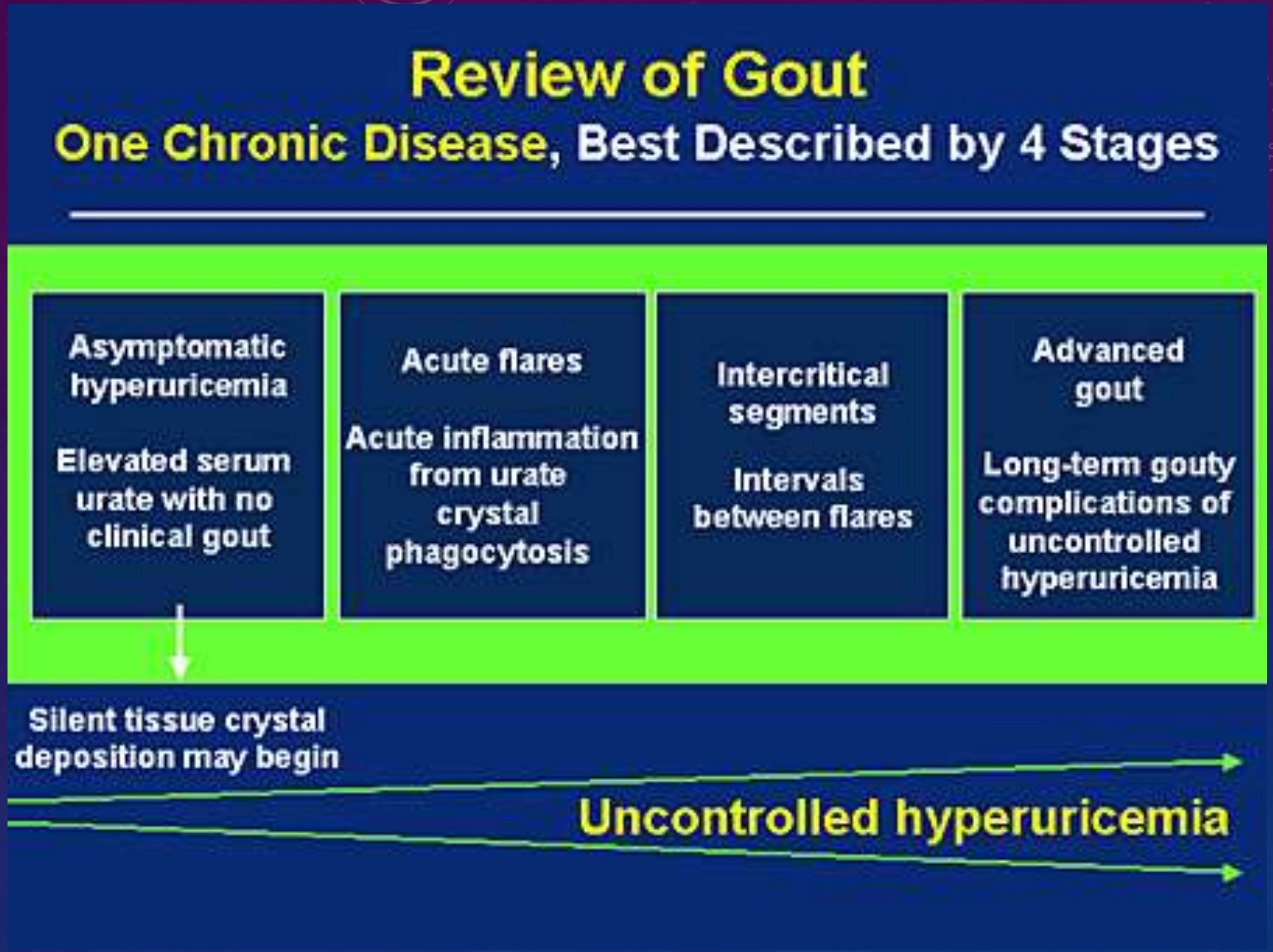
Desai J, Steiger S, Anders H-J. Molecular pathophysiology of gout. *Trends in Molecular Medicine*. 2017;23(8):756-768. doi:10.1016/j.molmed.2017.06.005

GOUT ETIOLOGY

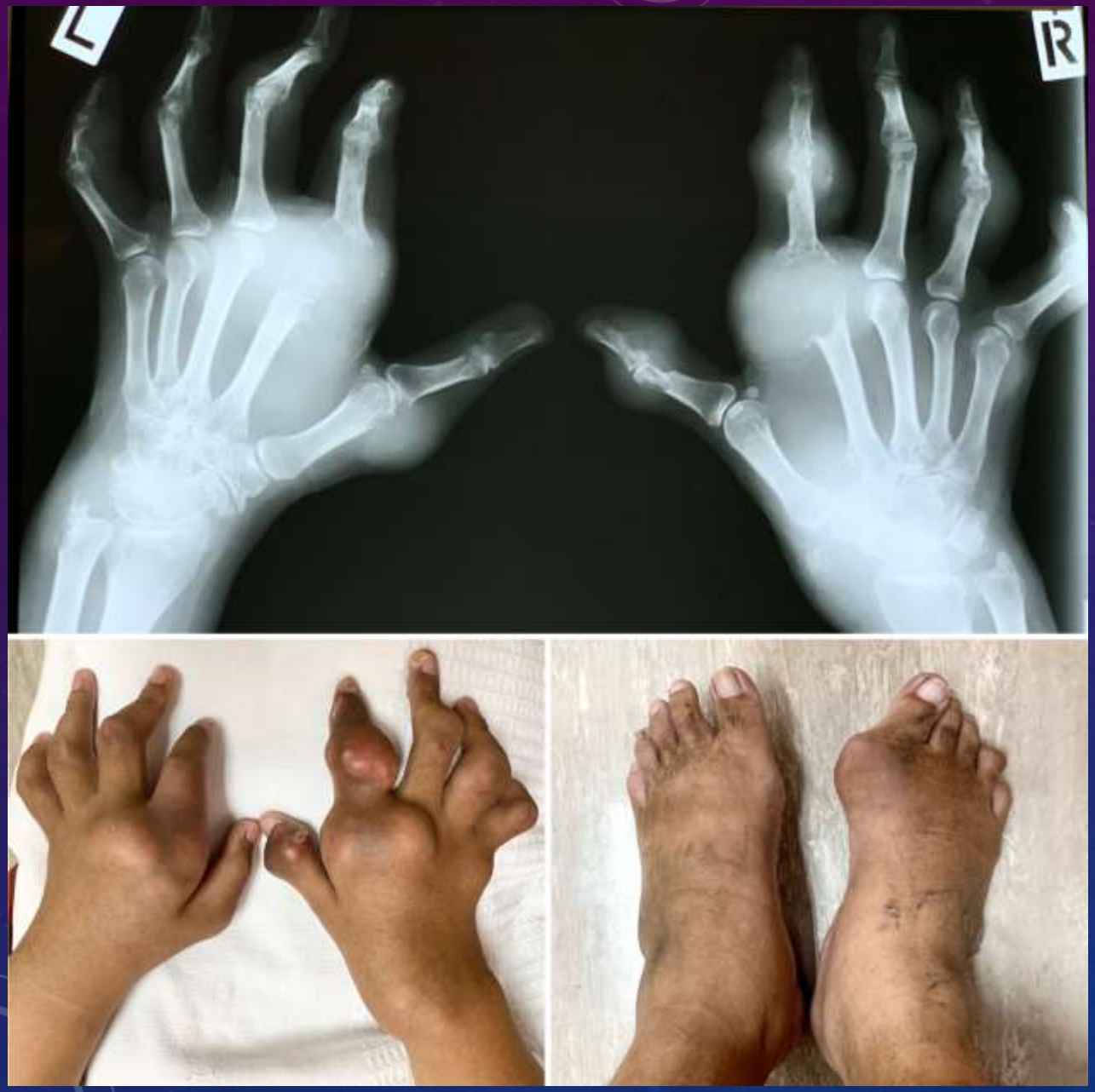
- Enzyme deficiencies → Endogenous overproduction
- Suspect Inherited if young man (< 25 yo) with early gout
  - X-linked: deficiency of Hypoxanthine-Guanine Phophoribosyltransferase (HGPRT)
    - Partial: Kelley-Seegmiller syndrome
    - Complete: Lesch Nyhan Syndrome
- Overactive Phosphoribosylpyrophosphate (PRPP) synthetase
- Glucose-6-phosphatase deficiency → Increased ATP breakdown and inhibited renal UA excretion during hypoglycemic events
- Fructose-1 Phosphate Aldolase Deficiency
- Tumor Lysis Syndrome, Psoriasis

GOUT ETIOLOGY

- Exogenous Overproduction:
  - High purine diet
  - ↑ hepatic ATP degradation from Fructose ingestion or Alcohol
  - ↑ nucleotide turnover in malignancies
- Underexcretion:
  - Renal insufficiency
  - Inhibited tubular UA secretion (ketoacidosis, lactic acidosis)
  - Lead nephropathy (saturnine gout)
  - Most common drug causes
    - CAN'T LEAP
    - Cyclosporine, Alcohol, Nicotinic Acid, Thiazides/Tacrolimus, Lasix/Loop diuretics, Ethambutol, Aspirin (low dose), Pyrazinamide
  - **Opposite** Uricosuric agents that can help lower UA:
    - Losartan, Amlodipine, Atorvastatin, Rosuvastatin, Fenofibrate, high dose Salicylates, Leflunomide



https://mobility-health.com/pages/gout-in-humans



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Tophi are MSU crystal deposits that accumulate over time in subchondral, synovial or subcutaneous areas.

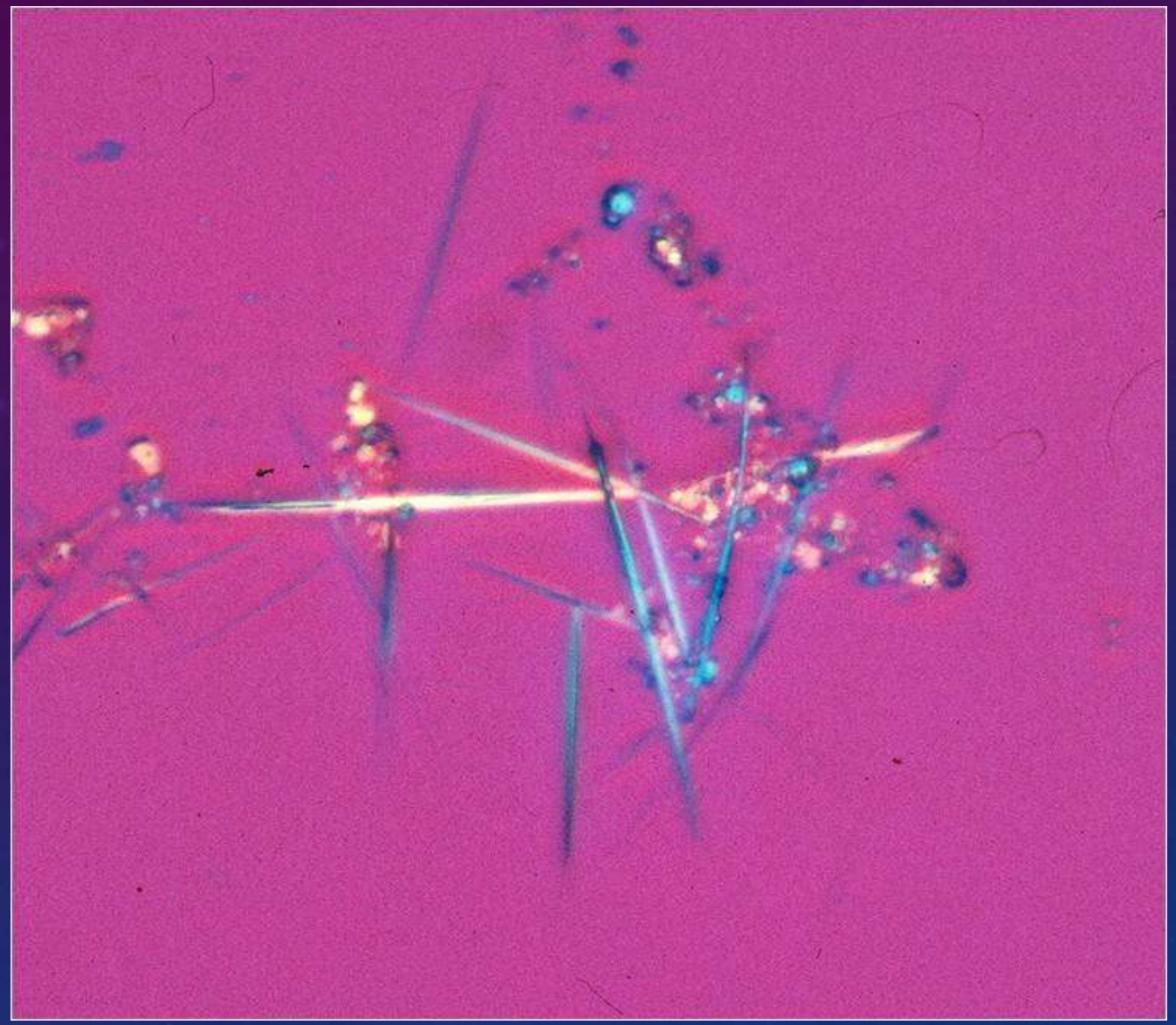
- Joints already with degenerative changes are a prime area for crystal formation to develop
- Tophi can occur in several locations: fingers, toes, extensor forearm, olecranon bursa, Achilles tendon, antihelix of ear.
- They can ulcerate chalky white material which are dense MSU crystals.
- Rarely can become infected.
- Over time, tophi may calcify and become apparent on X-rays.

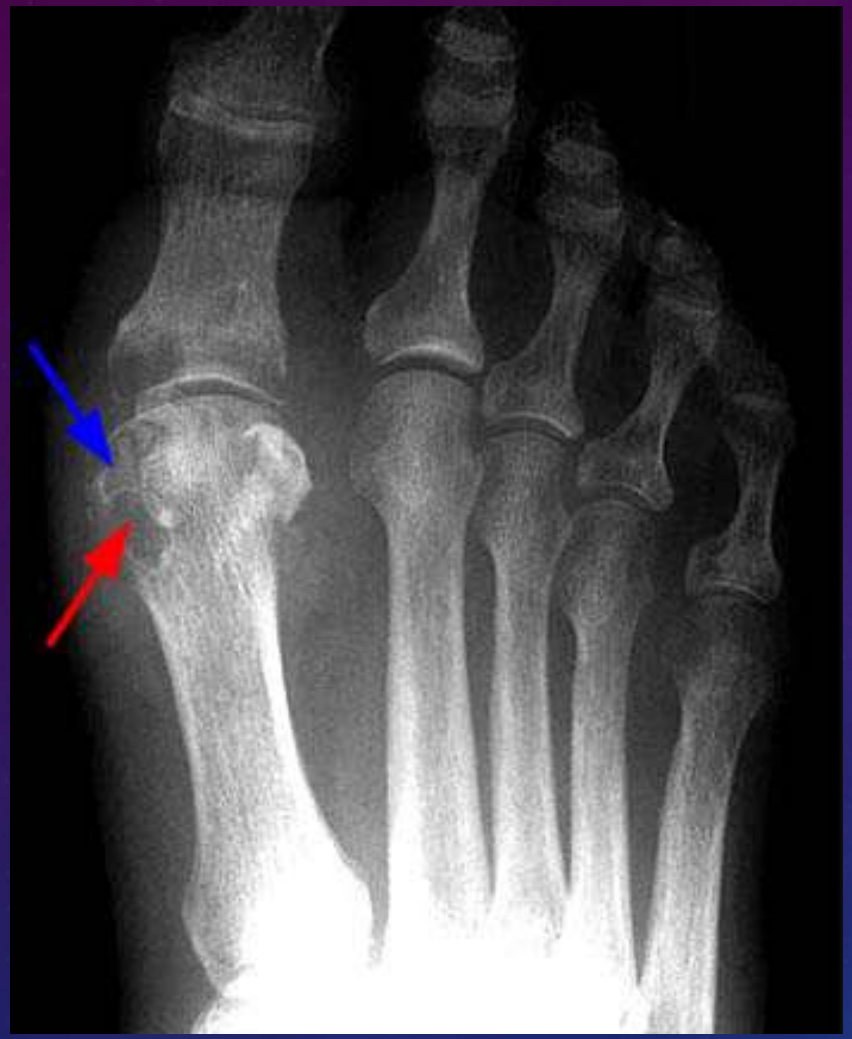
DIAGNOSIS OF GOUT

- Gold Standard: aspiration of synovial fluid or tophi revealing monosodium urate (MSU) crystals
  - Needle shaped, negatively birefringent (yellow in parallel to axis of red compensator) on polarized microscopy
  - Synovial fluid is inflammatory (20K-100K WBC/mm3) - mainly neutrophils
  - Always obtain culture along with crystals and cell count as infection can precipitate gout attack
- CANNOT use uric acid levels during flare to diagnose gout.
  - Serum UA tends to normalize during acute flare in a third of patients
  - Important to recognize one can have chronic hyperuricemia in the absence of gout

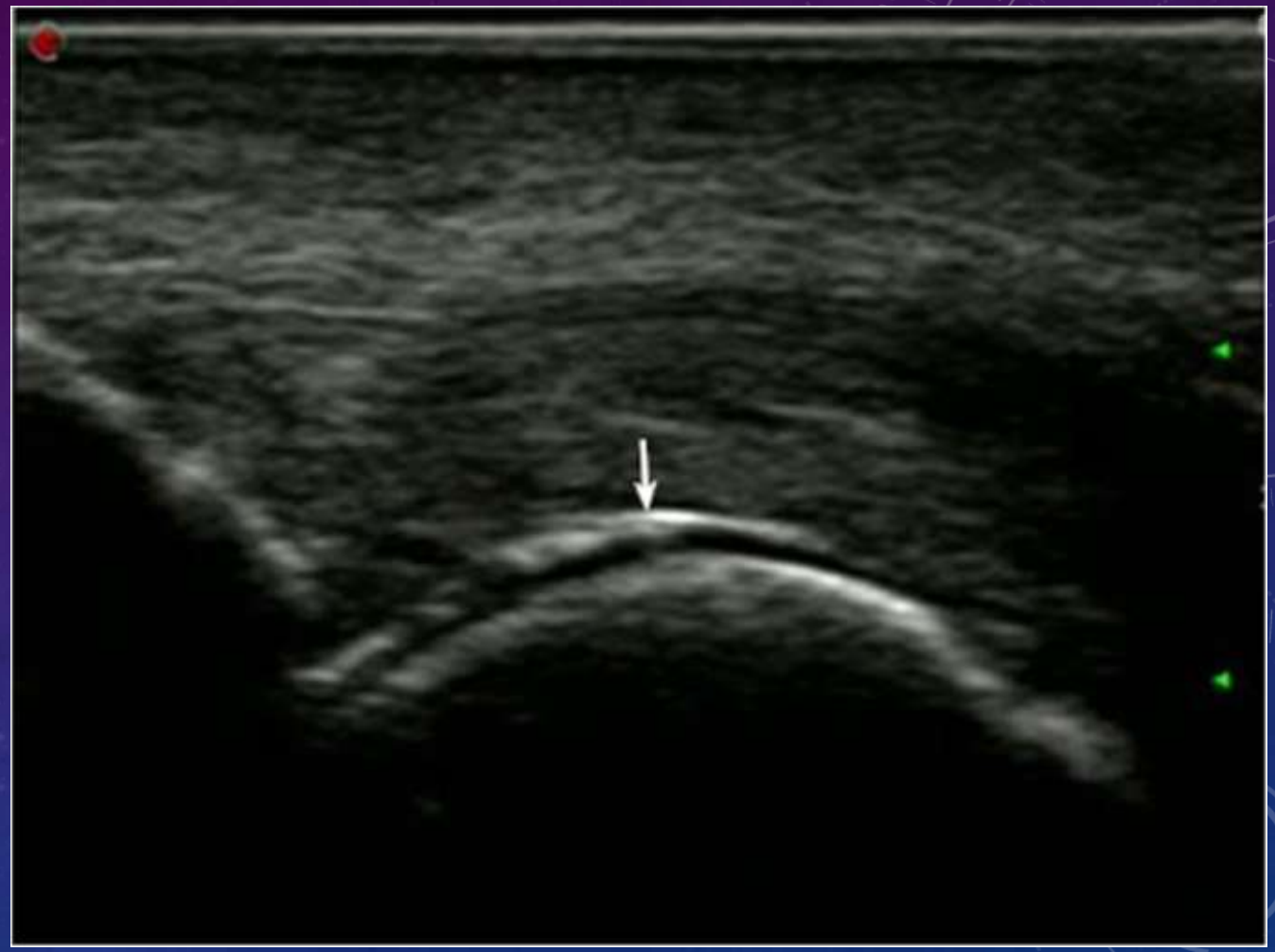
DIAGNOSIS OF GOUT

- X-ray with classic gout findings of punched out “rat-bite” erosion with overhanging edges. Do not typically see periarticular osteopenia unless late, progressed disease (as opposed to RA)
- Ultrasound with “double contour sign”
  - Operator dependent. But has 77% sensitivity and 84% specificity
- DECT scan to distinguish hard to diagnose gout vs other co-existing degenerative or inflammatory disease.





RadSource ©2022 https://radsource.us/gout/



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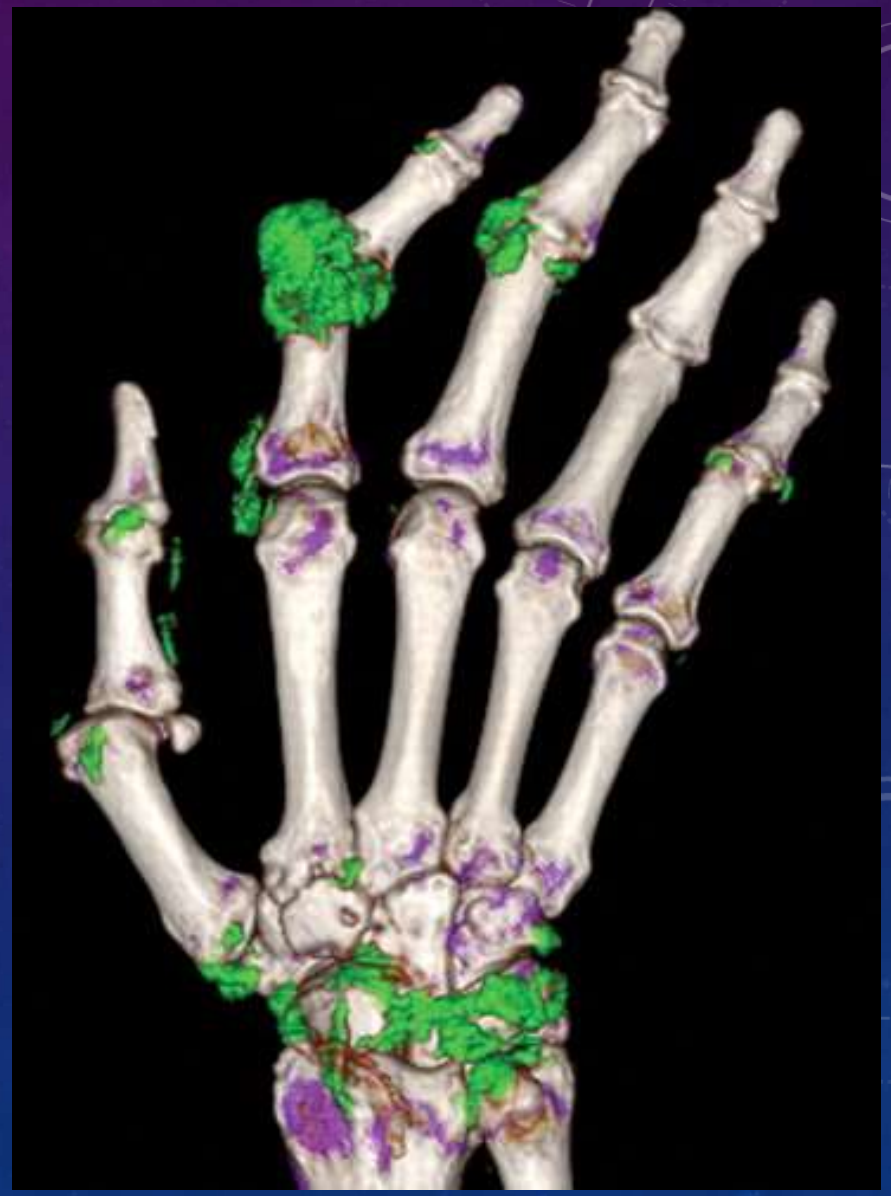
DECT – DUAL ENERGY CT SCAN

- Green for gout
- Purple for calcium
- Good modality if unable to aspirate joint, co-existing severe inflammatory or degenerative arthritis.
- False negatives reported in early gout
- False positives seen especially with degenerative arthritis
- 63% sensitivity/92% specificity
- Can be hard to find a facility that performs this imaging as it is relatively newer technology without vast indication as of yet.



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EXTRA-ARTICULAR MANIFESTATIONS OF GOUT

- Uric acid Nephrolithiasis – 10-25% gout patients
  - Uric acid stones radiolucent
  - Increased incidence of calcium stones in gout as well (uric acid is a nidus for calcium stone formation)
- Urate Nephropathy – MSU crystal deposition in renal interstitial tissue
  - Can cause low grade intermittent proteinuria, rare significant renal insufficiency
- Uric acid nephropathy – uric acid crystal precipitation in collecting ducts and ureters → acute renal failure
  - Especially in Tumor Lysis Syndrome after chemotherapy for leukemias or lymphomas

Glasnović M. Giht kao sustavna bolest: sistemske manifestacije i komorbiditeti u hiperuricemiji [Gout as a systemic disease: systemic manifestations and comorbidities of hyperuricaemia]. Reumatizam. 2012;59(2):119-32. Croatian. PMID: 23745468.

EXTRA-ARTICULAR MANIFESTATIONS OF GOUT

- Urate deposition has also been found in the following areas, leading to inflammation and chronic disease:
  - Myocardium[1]
  - Coronary Arteries
  - Prostate
- Uncontrolled gout has been found to be an independent risk factor for developing:[2]
  - Hypertension
  - Cardiovascular disease
  - Stroke
  - Chronic Kidney Disease
  - Metabolic syndrome.

1. Frustaci A, Russo MA, Sansone L, et al. Heart Failure From Gouty Myocarditis: A Case Report. Annals of Internal Medicine. 2019;172(5):363. doi:https://doi.org/10.7326/l19-0486
2. Glasnović M. Giht kao sustavna bolest: sistemske manifestacije i komorbiditeti u hiperuricemiji [Gout as a systemic disease: systemic manifestations and comorbidities of hyperuricaemia]. Reumatizam. 2012;59(2):119-32. Croatian. PMID: 23745468.

WHY DOES TREATING GOUT MATTER?

- 2021 Cohort study of > 250,000 ESRD patients in 2017 data found that those with gout compared to non-gout patients had higher comorbidity prevalence of Diabetes, HTN, Cardiovascular disease (HF, ischemic cardiomyopathy, PAD, CVA, acute MI, angina). In the year after gout diagnosis, risk of hospitalization was 11% higher and risk of mortality was 9% higher.[1]
- Presence of subcutaneous tophi was independently associated with increased risk of death from all causes as well cardiovascular causes (~3x increased risk of death).[2]
- For each increase in sUA by 1mg/dL, there was 9% increase in all-cause mortality and 20% increase in risk of coronary heart disease.[3]

1. Bleyer A, LaMoreaux B, Marder B, Kshirsagar O, Zhang Y. American Society of Nephrology: Kidney Week - abstract details. ASN News. https://www.asn-online.org/education/kidneyweek/2021/programabstract.aspx? controlId=3606120&utm_content=buffer20a45&utm_medium=social&utm_source=twitter.com&utm_campaign=buffer. Published November 4, 2021. Accessed January 12, 2022.
2. Vincent ZL, Gamble G, House M, et al. Predictors of Mortality in People with Recent-onset Gout: A Prospective Observational Study. The Journal of Rheumatology. 2016;44(3):368-373. doi:https://doi.org/10.3899/jrheum.160596
3. Zuo T, Liu X, Jiang L, Mao S, Yin X, Guo L. Hyperuricemia and coronary heart disease mortality: a meta-analysis of prospective cohort studies. BMC Cardiovascular Disorders. 2016;16(1). doi:https://doi.org/10.1186/s12872-016-0379-z

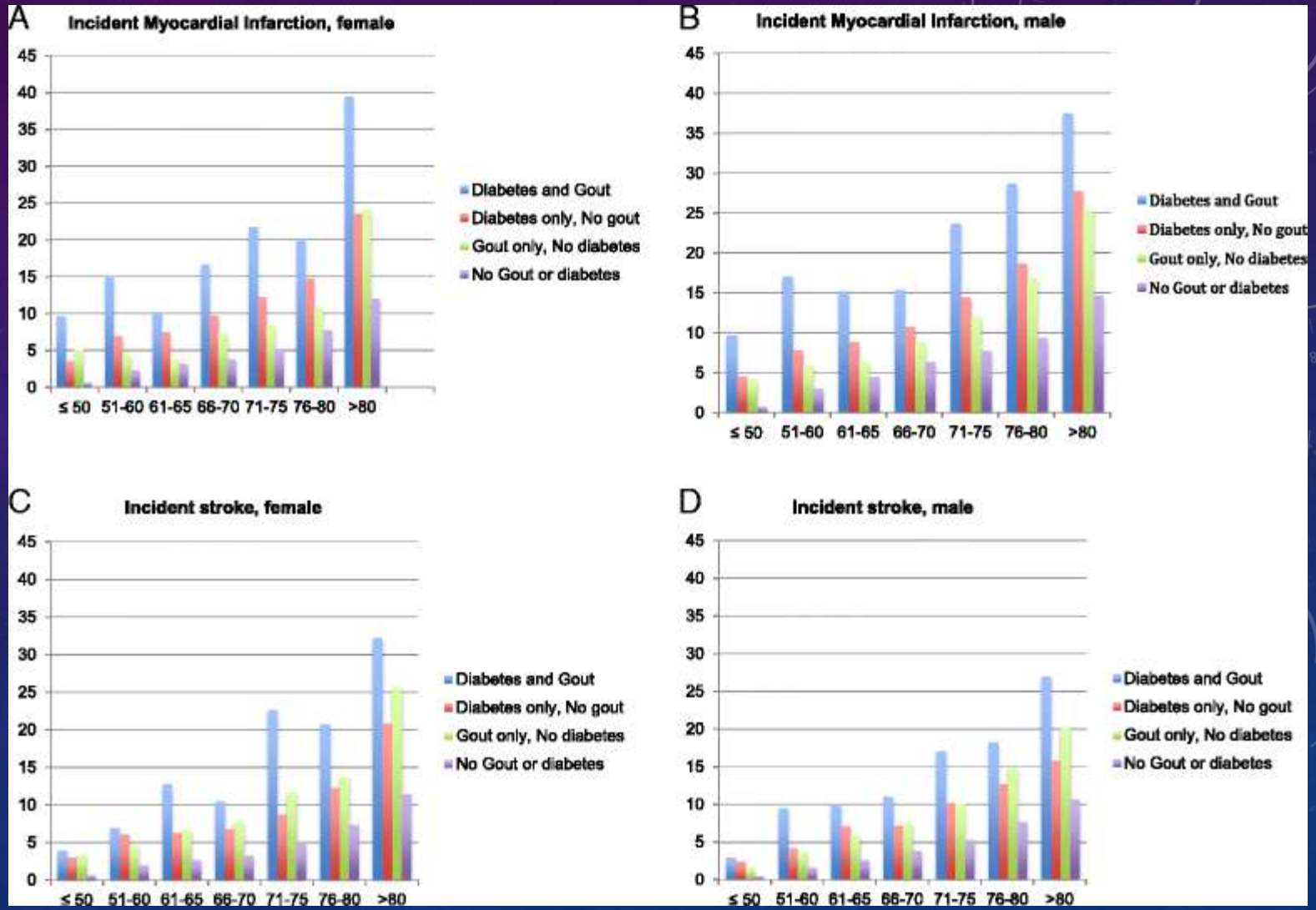
WHY DOES TREATING GOUT MATTER?

- Undertreated gout is an independent risk factor for developing:[1]
  - CAD, PAD
  - HTN
  - CHF
  - CKD
  - DM2

1. Bardin T, Richette P. Impact of comorbidities on gout and hyperuricaemia: an update on prevalence and treatment options. BMC Medicine. 2017;15(1). doi:https://doi.org/10.1186/s12916-017-0890-9

GOUT AS CV RISK EQUIVALENT TO DIABETES FOR STROKE

- Gout was an equivalent risk factor for incident stroke, compared to Diabetes
- Gout was not an equivalent risk factor for incident MI compared to Diabetes
- Gout in the setting of Diabetes, conferred 1.4x additive risk for MI and CVA compared to DM alone. Gout still an independent risk factor for MI.



Singh JA, Ramachandaran R, Yu S, et al. Is gout a risk equivalent to diabetes for stroke and myocardial infarction? A retrospective claims database study. Arthritis Research & Therapy. 2017;19(1). doi:https://doi.org/10.1186/s13075-017-1427-5

WHY DOES TREATING GOUT MATTER?

- Decreased survival of gout patients compared to those without gout due to numerous comorbidities.
- The natural progression of uncontrolled gout can lead to crippling deformities with decline in daily function and quality of life.
- Complications include both cardiovascular, metabolic and renal long term comorbidities, outside of gouty arthropathy.
- Therefore, it is important to not just treat the acute attacks, especially if more than one a year, as this is a chronic condition with lifelong need for urate lowering therapy to improve mortality.

WHEN TO START URATE LOWERING THERAPY?

- One or more tophi present on exam
- Any evidence of radiographic damage due to gout (ex: erosions on XR)
- More than one gout flare per year
- If only one gout flare but also have comorbidities such as CKD 3, Uric acid > 9 mg/dL, urolithiasis

- We do not treat asymptomatic hyperuricemia due lack of data thus far supporting this.

WHAT SHOULD OUR TREATMENT APPROACH BE?

- Treat to Target Serum Uric acid level < 6.
  - Titrate the urate lowering agent to this goal. Serial labs with sUA level q 2-4 weeks while monitoring patient for side effects until at goal.
- Always start an anti-inflammatory agent at the same time as the ULT
  - Anti inflammatory agent should be taken daily and continued for at least 3-6 months.
- Review modifiable risk factors: diet, diuretics, weight loss efforts, volume depletion, etc.
- Do not stop ULT during flares. Ultimately, the ULT, for most gout patients, will be a lifelong chronic medication as undertreated gout has increased risk of CV events as well as all cause mortality.

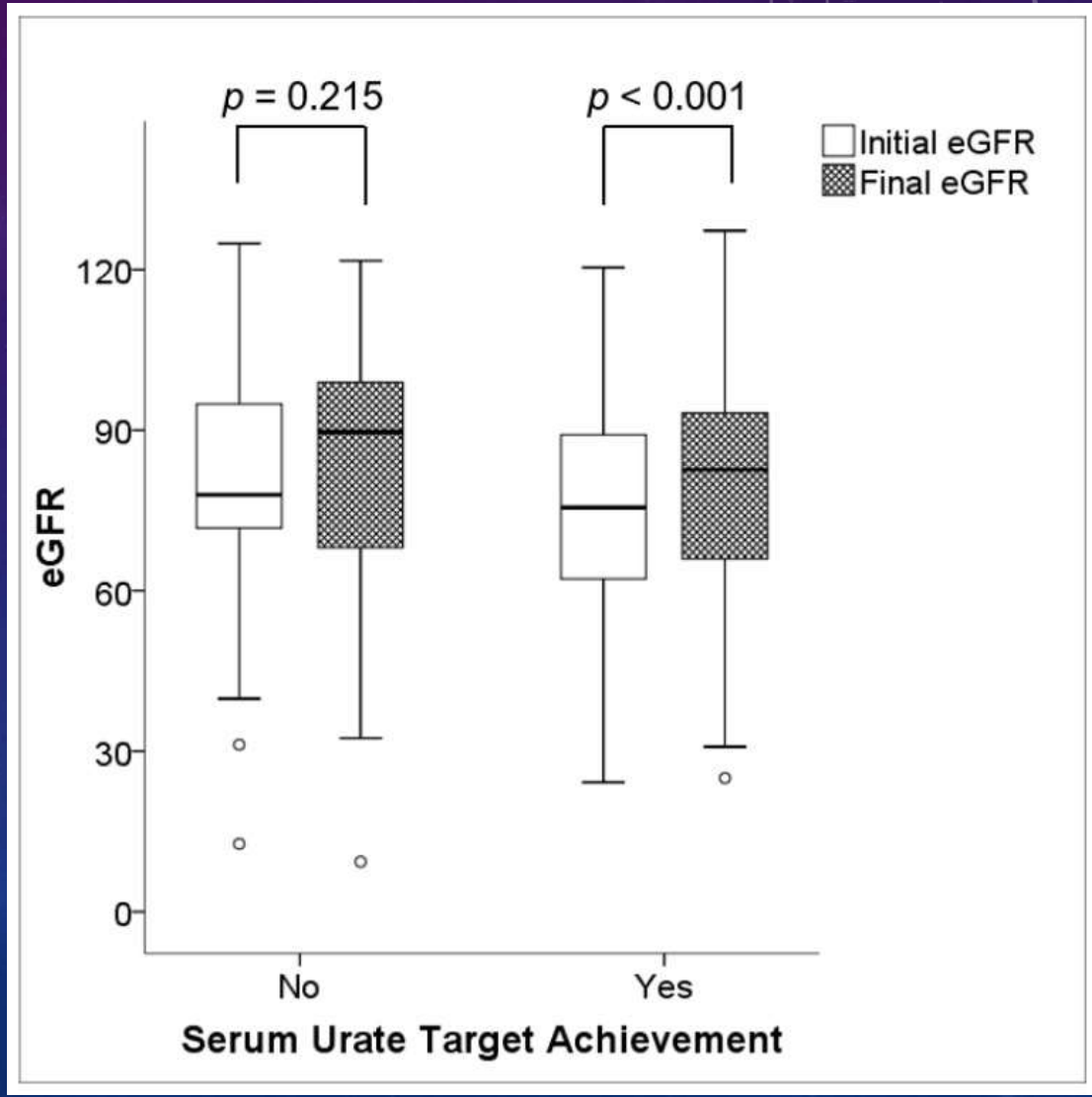
TREAT TO TARGET SERUM URIC ACID < 6 MG/DL

- In a 2021 Observational Study using causal inference approach of > 4,000 gout patients, there was a decreased rate of major adverse cardiac event (MACE) with a Treat to Target strategy for gout compared to only initiating urate-lowering therapy without targeting/monitoring uric acid levels/medication adherence.[1]

1. Yoshida K, Liu J, Solomon D, Glynn R, Kim S. Comparative Safety of Gout "Treat-to-target" and "Usual Care" Treatment Strategies on Cardiovascular Outcomes Using Observational Data: Causal Inference Approach [abstract]. Arthritis Rheumatol. 2021; 73 (suppl 10). https://acrabstracts.org/abstract/comparative-safety-of-gout-treat-to-target-and-usual-care-treatment-strategies-on-cardiovascular-outcomes-using-observational-data-causal-inference-approach/. Accessed January 12, 2022.

TREAT TO TARGET SERUM URIC ACID < 6 MG/DL

- There was no significant change in renal function (p = 0.215) in the population without serum urate target achievement; however, a significant improvement in renal function (p < 0.001) was demonstrated in the population with serum urate target achievement.



Kim WJ, Song JS, Choi ST. The Role of a "Treat-to-Target" Approach in the Long-Term Renal Outcomes of Patients with Gout. Journal of Clinical Medicine. 2019;8(7):1067. doi:https://doi.org/10.3390/jcm8071067

Arthritis Rheum. 2011 Dec;63(12):4002-6. doi: 10.1002/art.30649.

A two-stage approach to the treatment of hyperuricemia in gout: the "dirty dish" hypothesis

Fernando Perez-Ruiz [1], Ana Maria Herrero-Beites, Loreto Carmona

Affiliations + expand

PMID: 21898351 DOI: 10.1002/art.30649

Free article

Abstract

Objective: It is commonly accepted that the target serum urate level in patients receiving urate-lowering therapy for dissolution of urate crystals in hyperuricemia of gout is <6 mg/dl, and that patients with gout should continue urate-lowering therapy for the rest of their lives. This study was undertaken to reevaluate whether this stringent therapeutic target to dissolve crystals must be maintained lifelong to prevent new crystal formation.

Methods: In a prospective cohort of 211 patients with gout, urate-lowering therapy was withdrawn after 5 years if no tophus was present at baseline, or 5 years after resolution of the last tophus. Data on recurrence of gout and on serum urate levels and other potentially associated variables were analyzed.

Results: Multivariate regression analysis of time to crystal-proven recurrence of gout showed that serum urate levels during urate-lowering treatment and after its withdrawal were independently related to gout recurrence. None of the patients who had average serum urate levels of <7 mg/dl after urate-lowering therapy withdrawal developed a crystal-proven recurrence of gout. Post hoc analysis showed that weight loss and use of drugs that lower serum urate, such as losartan or fenofibrate, were associated with serum urate levels of <7 mg/dl during followup after urate-lowering therapy withdrawal; use of diuretics was associated with failure to achieve serum urate levels of <7 mg/dl during followup.

Conclusion: Our data support the hypothesis that after appropriate long-term treatment of hyperuricemia in gout with urate crystal dissolution being the therapeutic target, lifelong treatment can be targeted to achieve serum urate levels just below the threshold for saturation to avoid new crystal formation, similar to cleaning a dirty dish: more is required to get it clean than to keep it clean.

CAN WE START URATE LOWERING THERAPY DURING A FLARE?

Certain patient population where starting ULT at same time as acute gout flare is reasonable:

- Patient with good understanding of their gout health and understands the rationale between use of both anti-inflammatory and ULT in treatment regimen. Some mistake use as one or another and not the requirement of both.
- Documented baseline serum uric acid level outside of a flare, especially in those with hard to manage, perpetual flares.
- No significant underlying renal or hepatic comorbidity.
- It may be more prudent to start ULT once flare subsided in those w/ coexisting renal, hepatic and cardiac comorbidities in terms of watching for side effects, disease exacerbations. These tend to be a majority of the population.

Joint Bone Spine. 2015 Dec;82(6):428-31. doi: 10.1016/j.jbspin.2015.02.021. Epub 2015 Oct 9.

Significance of the initiation time of urate-lowering therapy in gout patients: A retrospective research

Xin Feng [1], Yao Li [2], Wei Gao [3]

Affiliations + expand

PMID: 26456042 DOI: 10.1016/j.jbspin.2015.02.021

Abstract

Objective: To evaluate the efficacy and safety of the initiation time of urate-lowering treatments (ULT) in gout patients.

Method: We retrospectively reviewed patients who were diagnosed with gout and were treated with ULT for at least 3 years. They were divided into two groups: group 1: 123 patients initiating ULT during an acute attack of gout; group 2: 457 patients prescribed ULT after an acute attack. Both demographic and clinical characteristics associated with gout were analyzed.

Results: Comparing patients in group 1 versus group 2: the former exhibited a shorter duration of gout (6.3±2.1 vs. 8.9±3.3 years). At the baseline, there was no significant difference in mean serum urate (SU; 7.8±1.4mg/dL vs. 7.9±1.9mg/dL, respectively). SU target levels (<6.0mg/dL) were achieved by 66.7 and 65.6% of the patients, respectively. The duration from initiation of ULT until the SU target was attained was lower in group 1 than in group 2. During the first 12 weeks, patients on ULT in group 1 had higher attack rates than those in group 2. The incidence of chronic kidney disease increased in percentage in group 1 was lower than in group 2.

Conclusions: Our survey revealed that in patients experiencing acute gout, initiation of ULT decreased the time required to reach the target SU and the incidence of CKD, but the attack rate was greater in the first 12 weeks.

Randomized Controlled Trial > J Clin Rheumatol. 2015 Apr;21(3):120-5.
doi: 10.1097/RHU.0000000000000235.

Does starting allopurinol prolong acute treated gout? A randomized clinical trial

Erica M Hill [1], Karen Sky, Michelle Sit, Angelique Collamer, Jay Higgs

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PMID: 25807090 DOI: 10.1097/RHU.0000000000000235

Abstract

Background: Traditionally, allopurinol is not initiated during an acute gout attack to avoid prolonging the painful arthritis. The 2012 American College of Rheumatology Guidelines for the Management of Gout suggest that urate-lowering therapy can be started during an acute attack, based on "consensus opinion of experts, case studies, or standard of care."

Objective: The aim of this study was to determine whether initiating allopurinol will adversely affect the resolution of acute, treated gout.

Methods: We conducted a 28-day, placebo-controlled, double-blind study of allopurinol initiation in patients with acute gout. Patients with crystal-proven gout by arthrocentesis were enrolled if they presented to the rheumatology clinic with an acute gout attack within 72 hours from initial therapy. The patients were also required to meet at least 1 additional criterion for urate-lowering therapy including (1) the presence of gouty tophi, (2) more than 1 acute gout attack per year, (3) a history of nephrolithiasis, or (4) urate overproduction (>1000 mg in 24-hour urine collection). Patients were excluded from the study if they had a glomerular filtration rate of less than 50 or liver function test of greater than 1.25 times the upper limit of normal. The treating physician determined therapy for the acute gout attack. Standard prophylaxis, with colchicine or nonsteroidal anti-inflammatory drugs, was prescribed. Allopurinol or placebo was initiated at 100 mg daily for the first 14 days and then increased to 200 mg daily for the next 14 days. The primary end point was protocol defined days to resolution of acute gout, incorporating patient-rated joint pain and physician examination. Secondary measures included Physician Global Assessment, patient-rated pain, adverse effects of therapy, and serum uric acid.

Results: Thirty-one patients (17 on placebo, 14 on allopurinol) completed the study. Both intent-to-treat and completer analyses showed only a statistically insignificant difference in days to resolution (15.4 days in the allopurinol group completers vs 13.4 days in the placebo group; P = 0.5). The secondary measures revealed that the acute phase of pain rapidly improved in both groups.

Conclusions: We initiated allopurinol at low doses during an acute gout attack in patients who met criteria for starting urate-lowering therapy and did not have abnormal kidney or liver function. In this cohort, allopurinol did not prolong the acute, treated attack.

Initiation of febuxostat for acute gout flare does not prolong the current episode: a randomized clinical trial

Ertao Jia, Yanying Zhang ✉, Wukai Ma, Bo Li, Hongling Geng, Li Zhong, Xueming Yao, Jingjing Xie, Yuya Xiao, Yubao Jiang ... Show more

Author Notes

Rheumatology, Volume 60, Issue 9, September 2021, Pages 4199–4204,
https://doi.org/10.1093/rheumatology/keaa908

Published: 06 January 2021 **Article history** ▾

Abstract

Objective

Our objective was to determine whether initiation of febuxostat during an acute gout flare prolongs the current episode.

Methods

In this randomized, placebo-controlled, single-blinded, multicentre trial, patients with acute gout flares within 72 h were randomized (1:1) to the placebo and febuxostat (40 mg/day) groups. All patients were administered diclofenac (150 mg/day) for 7 days and then open-labelled on the eighth day. Febuxostat 40 mg daily and diclofenac 75 mg daily were administered from day 8 through 28 for the remission period. The dose of diclofenac was 150 mg/day before

Results

We randomized 140 patients, 70 into each arm. The mean days to resolution was 5.98 days [median 7.00, interquartile range (IQR) 2.45 days] for the placebo and 6.50 days (median 7.00, IQR 3.67 days) for the febuxostat group ($P = 0.578$). The rate of resolution within 7 days was 84.38% for the placebo group and 76.92% for the febuxostat group ($P = 0.284$). There were no statistically significant differences in joint pain, swelling, tenderness and erythema scores at days 1, 3, 5 and 7. The mean serum uric acid levels were 507.54 and 362.62 μmol/l for the placebo and febuxostat group, respectively, on day 7 ($P = 0.000$). The rate of recurrent gout flares was 10.00% for the placebo group and 6.56% for the febuxostat group from day 8 through 28 ($P = 0.492$).

Conclusion

Initiation of febuxostat administration during an acute gout flare did not prolong the duration of acute flares.

Trial registration

Chinese Clinical Trial Registry, http://www.chictr.org.cn/, ChiCTR1800015962

Randomized Controlled Trial > Ann Rheum Dis. 2017 Sep;76(9):1522-1528.
doi: 10.1136/annrheumdis-2016-210872. Epub 2017 Mar 17.

A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout

Lisa K Stamp [1 2], Peter T Chapman [2], Murray L Barclay [1], Anne Horne [3], Christopher Frampton [1], Paul Tan [3], Jill Drake [1], Nicola Dalbeth [3]

Affiliations + expand

PMID: 28314755 DOI: 10.1136/annrheumdis-2016-210872

Abstract

Objectives: To determine the efficacy and safety of allopurinol dose escala serum urate (SU) approach.

Methods: A randomised, controlled, parallel-group, comparative clinical tr with gout receiving at least creatinine clearance (CrCL)-based allopurinol d ≥6 mg/dL were recruited. Participants were randomised to continue currer allopurinol dose escalation for 12 months. In the dose escalation group, al monthly until SU was <6 mg/dL. The primary endpoints were reduction in (AEs).

Results: 183 participants (93 control, 90 dose escalation) were recruited. At baseline, mean (SD) urate was 7.15 (1.6) mg/dL and allopurinol dose 269 mg/day. 52% had CrCL<60 mL/min. Mean changes in SU at the final visit were -0.34 mg/dL in the control group and -1.5 mg/dL in the dose escalation group (p<0.001) with a mean difference of 1.2 mg/dL (95% CI 0.67 to 1.5, p<0.001). At month 12, 32% of controls and 69% in the dose escalation had SU <6 mg/dL. There were 43 serious AEs in 25 controls and 35 events in 22 dose escalation participants. Only one was considered probably related to allopurinol. Five control and five dose escalation participants died; none was considered allopurinol related. Mild elevations in LFTs were common in both groups, a few moderate increases in gamma glutamyl transferase (GGT) were noted. There was no difference in renal function changes between randomised groups.

Conclusions: Higher than CrCL-based doses of allopurinol can effectively lower SU to treatment target in most people with gout. Allopurinol dose escalation is well tolerated.

GOUT TREATMENT: ACUTE FLARE AND PROPHYLAXIS

- Colchicine 1.2mg x 1 at beginning of flare followed by 0.6mg 1 hour later.
- Colchicine 0.6mg QD or BID for 3-6 months thereafter depending on concomitant meds.
- It is safe in CKD with dosing changes if GFR < 30mL/min.
- Avoid in those w/ concurrent CKD and severe hepatic disease.

GOUT TREATMENT: ACUTE FLARE AND PROPHYLAXIS

- NSAIDs in those who can tolerate them (not for CKD, recent PUD, recent cardiac stent/CABG)
  - Consider concomitant gastroprotection.
  - Ibuprofen 800mg TID. But avoid in those who need low dose Aspirin. Ibuprofen specifically may counteract the cardioprotective effects of Aspirin.
  - Naproxen 500mg BID
  - Indomethacin 50mg TID
  - Sulindac 200mg BID, Etodolac 400mg TID, Diclofenac 50mg TID or 75mg BID
  - Meloxicam 15mg/d
  - Celecoxib 200mg BID (may be beneficial for those with gastritis/PUD history as a selective COX-2 inhibitor)

GOUT TREATMENT: ACUTE FLARE AND PROPHYLAXIS

- Glucocorticoids – roughly 0.5-1 mg/kg at start of flare in those who cannot take NSAIDs, Colchicine, etc.
  - If inpatient, I personally like Solumedrol 80mg IV x 1, followed by PO Prednisone 40mg/d x 2-3 days, 30mg/d x 2-3 days, 20mg/d x 2-3 days, 10mg/d x 2-3 days, then stop.
  - If outpatient, just the oral portion of steroid taper.
  - For prophylaxis, Prednisone 5-10 mg/day.
  - Intra-articular only when you are VERY sure there is no underlying infection.

GOUT TREATMENT: ACUTE FLARE AND PROPHYLAXIS

- Canakinumab – IL-1β inhibitor by binding it to block interaction with its IL-1 receptor.
  - FDA approved as of August 2023 for adults in whom the following were contraindicated/intolerant to/inadequate responders to: NSAIDs, Colchicine, repeated courses of steroids
  - 150mg subq x 1 ASAP at start of attack. It has a long half life of about 26 days.
  - If retreatment required, can give after at least 12 weeks from prior dose.
  - Was found to be superior to Triamcinolone in acute gout and superior to Colchicine in gout prophylaxis.

GOUT TREATMENT: ACUTE FLARE AND PROPHYLAXIS

- Anakinra - IL-1 Receptor antagonist.
  - Used off-label for treatment of acute gout
  - Use if Colchicine, NSAIDs, steroids, Canakinumab is not tolerated or contraindicated
  - Daily subq injection with high incidence of injection site reactions.
  - Increased risk of serious infections, neutropenia, although rare.

CHRONIC GOUT MANAGEMENT – URATE LOWER THERAPY

- 1st Line Treatment: Allopurinol = purine-like Xanthine Oxidase Inhibitor (XOI).
- Start low and up-titrate slowly to goal sUA.
  - Start at 100mg/day and up-titrate every few weeks based on sUA. If GFR < 30, start at 50mg/d.
  - Some patients may need as high as 900mg/d of Allopurinol. As long as labs are monitored, don't be afraid to push it. Half of patients do not achieve sUA < 6 at 300mg/d dose Allopurinol.
  - Two main causes of inadequate response to Allopurinol are
    - Poor Adherence
    - Under-dosed Allopurinol.
  - Can screen for HLA-B*5801 allele in susceptible populations (Asians, African Americans) as it has 150-500x increased risk for Allopurinol Hypersensitivity Syndrome. If positive, use Febuxostat first instead.

CHRONIC GOUT MANAGEMENT

- 2nd Line Treatment: Febuxostat = non-purine selective XOI.
  - Start around 40mg/d and uptitrate to 80mg/d if needed. Safe in CKD but limit to 40mg/d if GFR < 30
- If Allopurinol not effective/tolerated or contraindicated.
- 2nd line due to cost, and some cardiovascular concerns.
  - CVD Black Box warnings. Try other oral ULT in those with known CVD before Febuxostat. However, the trial studying this for Febuxostat had several flaws.

- Any XOI and Azathioprine/Mercaptopurine drug interaction → higher levels of the immunosuppressant as AZA/MP are metabolized by XO. Avoid this combination as much as possible or use lower doses of the immunosuppressant if necessary.

Randomized Controlled Trial > N Engl J Med. 2018 Mar 29;378(13):1200-1210.
doi: 10.1056/NEJMoa1710895. Epub 2018 Mar 12.

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

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Collaborators, Affiliations + expand

PMID: 29527974 DOI: 10.1056/NEJMoa1710895

Free article

Abstract

Background: Cardiovascular risk is increased in patients with gout. We compar outcomes associated with febuxostat, a nonpurine xanthine oxidase inhibitor, v with allopurinol, a purine base analogue xanthine oxidase inhibitor, in patients cardiovascular disease.

Methods: We conducted a multicenter, double-blind, noninferiority trial involv and cardiovascular disease; patients were randomly assigned to receive febuxo were stratified according to kidney function. The trial had a prespecified noninferiority margin of 1.3 for the hazard ratio for the primary end point (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or unstable angina with urgent revascularization).

Results: In total, 6190 patients underwent randomization, received febuxostat or allopurinol, and were followed for a median of 32 months (maximum, 85 months). The trial regimen was discontinued in 56.6% of patients, and 45.0% discontinued follow-up. In the modified intention-to-treat analysis, a primary end-point event occurred in 335 patients (10.8%) in the febuxostat group and in 321 patients (10.4%) in the allopurinol group (hazard ratio, 1.03; upper limit of the one-sided 98.5% confidence interval [CI], 1.23; P=0.002 for noninferiority). All-cause and cardiovascular mortality were higher in the febuxostat group than in the allopurinol group (hazard ratio for death from any cause, 1.22 [95% CI, 1.01 to 1.47]; hazard ratio for cardiovascular death, 1.34 [95% CI, 1.03 to 1.73]). The results with regard to the primary end point and all-cause and cardiovascular mortality in the analysis of events that occurred while patients were being treated were similar to the results in the modified intention-to-treat analysis.

Conclusions: In patients with gout and major cardiovascular coexisting conditions, febuxostat was noninferior to allopurinol with respect to rates of adverse cardiovascular events. All-cause mortality and cardiovascular mortality were higher with febuxostat than with allopurinol. (Funded by Takeda Development Center Americas; CARES ClinicalTrials.gov number, NCT01101035 .).

Randomized Controlled Trial > Lancet. 2020 Nov 28;396(10264):1745-1757.
doi: 10.1016/S0140-6736(20)32234-0. Epub 2020 Nov 9.

Long-term cardiovascular safety of febuxostat compared with allopurinol in patients with gout (FAST): a multicentre, prospective, randomised, open-label, non-inferiority trial

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Abstract

Background: Febuxostat and allopurinol are urate-lowering therapies used to treat patients with gout. Following concerns about the cardiovascular safety of febuxostat, the European Medicines Agency recommended a post-licensing study assessing the cardiovascular safety of febuxostat compared with allopurinol.

Methods: We did a prospective, randomised, open-label, blinded-endpoint, non-inferiority trial o febuxostat versus allopurinol in patients with gout in the UK, Denmark, and Sweden. Eligible patie were 60 years or older, already receiving allopurinol, and had at least one additional cardiovascul risk factor. Those who had myocardial infarction or stroke in the previous 6 months or who had severe congestive heart failure or severe renal impairment were excluded. After a lead-in phase in which allopurinol dose was optimised towards achieving a serum urate concentration of less than 0·357 mmol/L (<6 mg/dL), patients were randomly assigned (1:1, with stratification according to previous cardiovascular events) to continue allopurinol (at the optimised dose) or start febuxostat at 80 mg/day, increasing to 120 mg/day if necessary to achieve the target serum urate concentration. The primary outcome was a composite of hospitalisation for non-fatal myocardial infarction or biomarker-positive acute coronary syndrome; non-fatal stroke; or cardiovascular death. The hazard ratio (HR) for febuxostat versus allopurinol in a Cox proportional hazards model (adjusted for the stratification variable and country) was assessed for non-inferiority (HR limit 1·3) in an on-treatment analysis. This

Findings: From Dec 20, 2011, to Jan 26, 2018, 6128 patients (mean age 71·0 years [SD 6·4], 5225 [85·3%] men, 903 [14·7%] women, 2046 [33·4%] with previous cardiovascular disease) were enrolled and randomly allocated to receive allopurinol (n=3065) or febuxostat (n=3063). By the study end date (Dec 31, 2019), 189 (6·2%) patients in the febuxostat group and 169 (5·5%) in the allopurinol group withdrew from all follow-up. Median follow-up time was 1467 days (IQR 1029-2052) and median on-treatment follow-up was 1324 days (IQR 870-1919). For incidence of the primary endpoint, on-treatment, febuxostat (172 patients [1·72 events per 100 patient-years]) was non-inferior to allopurinol (241 patients [2·05 events per 100 patient-years]; adjusted HR 0·85 [95% CI 0·70-1·03], p<0·0001). In the febuxostat group, 222 (7·2%) of 3063 patients died and 1720 (57·3%) of 3001 in the safety analysis set had at least one serious adverse event (with 23 events in 19 [0·6%] patients related to treatment). In the allopurinol group, 263 (8·6%) of 3065 patients died and 1812 (59·4%) of 3050 had one or more serious adverse events (with five events in five [0·2%] patients related to treatment). Randomised therapy was discontinued in 973 (32·4%) patients in the febuxostat group and 503 (16·5%) patients in the allopurinol group.

Interpretation: Febuxostat is non-inferior to allopurinol therapy with respect to the primary cardiovascular endpoint, and its long-term use is not associated with an increased risk of death or serious adverse events compared with allopurinol.

CHRONIC GOUT MANAGEMENT

- Probenecid = Uricosuric that promotes uric acid excretion via inhibition of URAT-1 and GLUT-9 in renal tubules.
  - Used best when added onto a XOI.
  - AVOID if GFR < 50 due to lack of efficacy.
  - CONTRAINDICATIONS: nephro/urolithiasis, concomitant salicylates (Aspirin decreases effectiveness of Probenecid)
  - Numerous drug interactions and can increase serum concentrations of NSAIDs, many antibiotics, sulfonylureas, Heparin, Dapsone, Methotrexate, etc.

CHRONIC GOUT MANAGEMENT

- Pegloticase = Recombinant pegylated Uricase which converts uric acid into Allantoin (5-10x more soluble)
  - IV q 2 wks. Cost-prohibitive also, therefore not 1st or 2nd line unless failed others and/or significant tophi burden.
  - CONTRAINDICATION: G6PD deficiency → increased risk of hemolytic anemia and methemoglobinemia. All must be screened for this prior to administration.
  - Highly effective medication and can take sUA levels down to undetectable.
  - Gout flare prophylaxis is mandatory as well as pretreatment with antihistamines, acetaminophen and steroids (if needed).
  - High rate of developing anti-pegloticase antibodies which are associated with anaphylactic infusion reactions. Check sUA prior to every infusion. If sUA rising > 6 prior two consecutive infusions, med is discontinued.
    - This risk is significantly diminished with concomitant use of DMARD therapy (ex: Methotrexate, Mycophenolate) to prevent antibody formation

ADJUNCTIVE LIFESTYLE AND OTHER RISK MODIFICATIONS

- Adjunct because > 80% gout due to urate underexcretion, not overproduction! Dietary changes will not have as much of an impact as pharmacotherapy itself.
- Weight loss efforts – obesity is a risk factor
- Treat any underlying Hyperparathyroidism, Hypothyroidism
- Avoid volume depletion, stay well hydrated
- Avoid alcohol
  - Recent data suggests that among those w/ established gout, episodic consumption of all alcohol types increases the risk of recurrent flare in a dose-dependent fashion.
- Avoid High Fructose Corn Syrup and sugary drinks like sodas
- Avoid high purine diets: red meat, shellfish, fatty poultry, organ meats, etc.
- Consider reducing high fat dairy from diet.

LIFESTYLE AND OTHER RISK MODIFICATIONS

- There is insufficient evidence or insignificant improvement with:
  - Adding Vitamin C supplements
    - Small studies thus far showed clinically insignificant changes in sUA concentrations.
  - Cherries, cherry extract
    - May contain anti-oxidants and anti-inflammatory properties but no evidence thus far regarding urate lowering ability especially compared to proven pharmacology.

OTHER RISK MODIFICATIONS

- Most common drug causes
  - “CAN’T LEAP” mnemonic
  - Cyclosporine, Alcohol, Nicotinic Acid, Thiazides/Tacrolimus, Lasix/Loop diuretics, Ethambutol, Aspirin (low dose), Pyrazinamide

- On the other hand, Uricosuric agents that can help lower sUA:
  - Losartan, Amlodipine, Atorvastatin, Rosuvastatin, Fenofibrate, high dose Salicylates, Leflunomide

FINAL THOUGHTS ON GOUT MANAGEMENT

- DO treat gout as a chronic condition with Treat to Target strategy. Monitor serum uric acid levels to target < 6 while titrating ULT.
- DO start anti-inflammatories during new gout flares and keep for at least 3-6 months while titrating ULT to target serum uric acid goals.
- Undertreated gout is an independent risk factor for cardiovascular, renal and metabolic co-morbidities.
- Stopping ULT in well controlled patients may cause recurrent gout flares with potential for permanent consequences. Continue ULT indefinitely at lowest dose necessary to keep serum UA at goal. If therapy is well tolerated and not burdensome, ULT should continue lifelong for comorbidity risk management.

1. A 53 year old white male presents to your office with a warm left knee effusion ongoing for the past two days that began abruptly, awakening him from sleep. This is the second time this has happened this year. He has a history of CKD 3b, Hypertension, Nephrolithiasis, and a BMI of 39. He eats red meat and pork. He does not drink alcohol. Serum urate level is 5.4 mg/dL. Knee synovial fluid crystal analysis demonstrates needle shaped, negatively birefringent crystals on polarized microscopy. Which of the following would be the best initial recommended urate lowering therapy in this patient?

a. Allopurinol
b. Febuxostat
c. Probenecid
d. Anakinra

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2. This 53 year old white male returns to your office four weeks later while on Allopurinol 300mg/d and Colchicine 0.6mg BID. He reports continued intermittent swelling of his left knee. CBC and CMP are stable. Serum urate level outside of a flare was 9.3 mg/dL. Currently, the serum urate level is 7.9 mg/dL. What is the next best step in regards to the urate lowering therapy?

a. Switch from Allopurinol to Febuxostat
b. Slowly up-titrate Allopurinol by 50-100mg until at serum urate goal.
c. Do nothing with the Allopurinol. Give a steroid pack instead.

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3. When starting urate lowering therapy, one should also start a prophylactic anti-inflammatory agent concomitantly which will be continued daily for at least 3-6 months.

a. True
b. False

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b. False

4. Gout lab monitoring is as follows:

a. Regular lab monitoring of gout is not required
b. Check serum urate once at initiation of therapy, then every six months to yearly.
c. Every 2 to 5 weeks initially and then every 6 months thereafter, with a serum urate goal of <6 mg/dL.

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5. Complications of untreated or undertreated gouty arthritis include not just increased risk of crippling deformities, but also cardiovascular and renal comorbidities.

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