Evidence Based Medicine and the Treatment of Gout

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CONFLICT OF INTEREST

- I have no conflicts of interest pertaining to the material presented in this lecture.

OUTLINE

- Gout from a Podiatric Physicians Perspective
- Gout from a Rheumatologists Perspective

OUTLINE

- **Gout from a Podiatric Physicians Perspective**
  - Clinical Presentation
  - Differential Diagnosis
  - Risk Factors
  - Clinical / Lab findings
  - Radiographic Features
  - Non Medical Treatment
  - When to Refer

OUTLINE

- **Gout from a Rheumatologist Perspective**
  - Treatment of Patient with Acute Gout Flare
    - Colchicine
    - Corticosteroids
    - Indocin/NSAID's
  - Long-term Management of Gout
  - Peri-operative Management of the Gout Patient
  - Management of the Recalcitrant Patient
    - Newer Medication Options
      - Lesinurad/Allopurinol
      - Krystexxa

Famous Sufferers of Gout

- Leonardo da Vinci 1519
- King Henry VIII 1547
- Charles V 1558
- Nostradamus 1566
- Sir Isaac Newton 1727
- Benjamin Franklin 1790
- Beethoven 1827
- Luciano Pavarotti

The Severe Gout of Holy Roman Emperor Charles V

Jaume Ordi, M.D., Pedro L. Alonso, M.D., Julian de Zulueta, M.D., Jordi Esteban, M.D., Martin Velasco, M.D., Ernest Mas, M.D., Elias Campo, M.D., and Pedro L. Fernández, M.D.

N Engl J Med 2006;355:516-520. Aug 2006

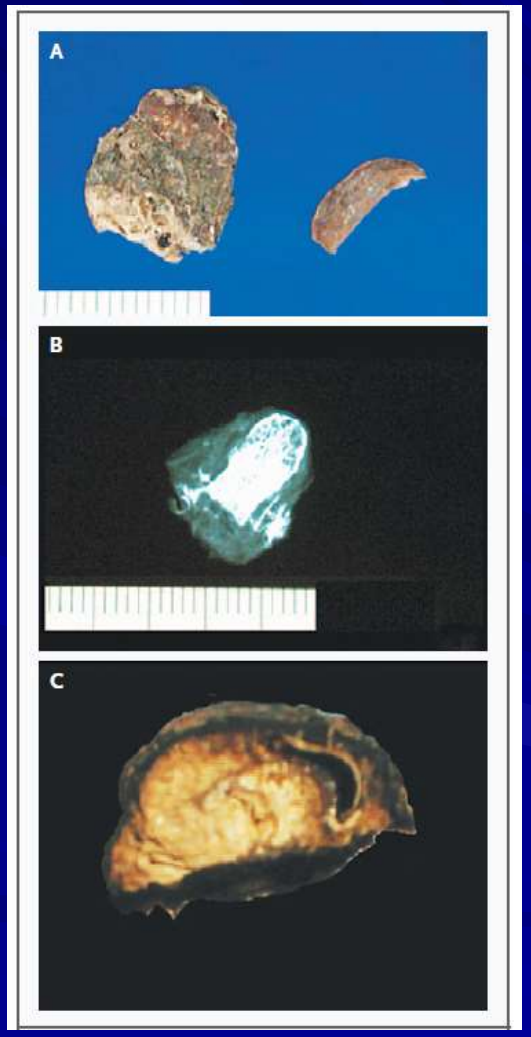
King Charles V 1500-1558

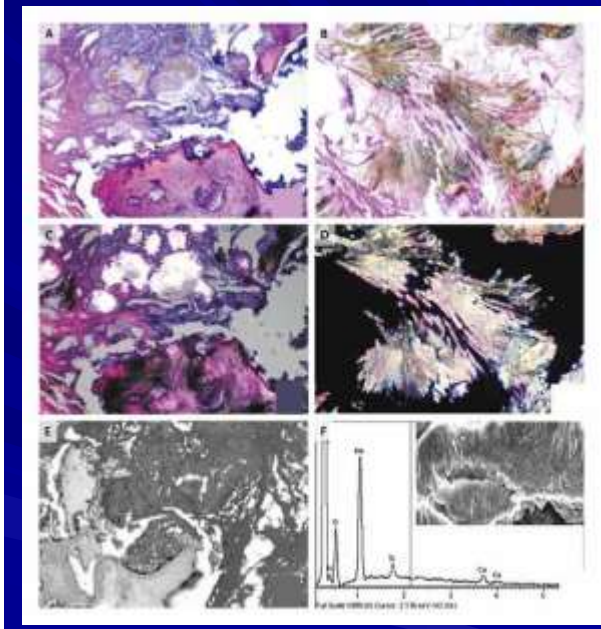
- Holy Roman Emperor.
  - Abdicated throne due to effects of gout.
- Emperor had a voracious appetite, especially for meat.
- Drank large quantities of beer and wine.
  - Ordered a specially designed four-handed drinking mug.

N Engl J Med 2006;355:516-520. Aug 2006

King Charles V 1500-1558

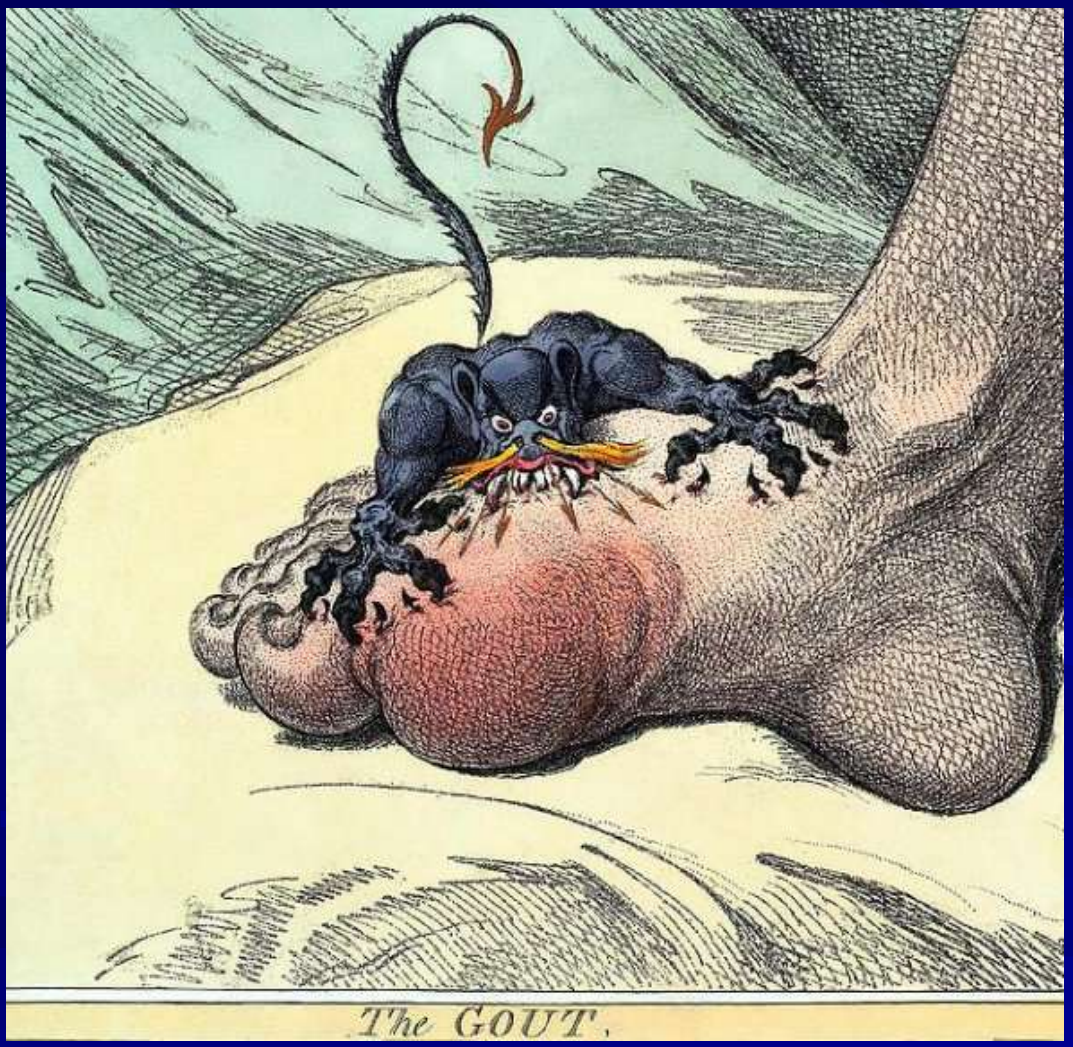
- Pathological analysis of distal phalanx of fifth digit of hand was performed.
- Radiograph demonstrated erosive changes as well as soft-tissue calcification
- Massive chalky appearing soft tissue mass confirmed gout crystals via electron microscopy.





N Engl J Med 2006;355:516-520. Aug 2006

James Gillray 1756-1815



1799

- British caricaturist and printmaker
- 18th Century
- Considered to be the Father of Political Cartoons

Feb 1805. Napoleon vs. William Pitt

Depicts England and France carving up the world.

James Gillray 1756-1815

ray himself became
alcoholic and suffered
n Gout.

GOUT

- Arthritic process which occurs secondary to hyperurecemia.
  - Overproducers
  - Under-excretors
- Estimated that greater than 5 Million people in the United States are affected by Gout.

- … Interesting fact:
- Not everyone with hyperuricemia develops gout – up to two-thirds of people with hyperuricemia never develop symptoms.

Epidemiology

- Males > Females 10:1 ratio
- Highest incidence is in 5th decade of life
- African Americans greater incidence than Caucasians
- Rare in pre-menopausal females
  - Estrogen promotes the excretion of uric acid
  - Post menopausal: Male:Female 3:1 ratio
- Most common cause of inflammatory arthritis in males > 30 years of age

Is the Incidence of Gout Rising?

- There was a greater than 2-fold increase in the rate of primary gout (i.e., no history of diuretic exposure) in the recent compared to the older time periods ($p = 0.002$). The incidence of secondary, diuretic related gout did not increase over time ($p = 0.140$).
- **Our results indicate that the incidence of primary gout has increased significantly over the past 20 years. While this increase might be a result of improved ascertainment of atypical gout, it may also be related to other, as yet unidentified, risk factors.**

Epidemiology of gout: is the incidence rising?
J Rheumatol. 2002 Nov;29(11):2403-6.
Arromdee E, Michet CJ, Crowson CS, O'Fallon WM, Gabriel SE.

Is the Incidence of Gout Rising?

- 2006-2014 a 26.8% increase in Acute Gout being primary presenting diagnosis.
- Men responsible for 78% of visits.

J Charnow: Emergency Department Gout Visits Rise Dramatically. Renal and Urology News. June, 2018.

GOUT RISK FACTORS

- Obesity
- High Blood Pressure
- Chronic Kidney Disease
- EtOH
- Diet (Purine rich foods)
- Medications
  - Diuretics
- Fasting
- Myelo-lymphoproliferative disorders
- Hypothyroidism
- Dehydration

MEDICATIONS

- **SPEED**
  - **S**alicylates
  - **P**yrazinamide (TB)
  - **E**thambutol (TB)
  - **E**thanol
  - **D**iuretics

Causes of hyperuricemia due to increased purine biosynthesis and/or urate production

Inherited enzyme defects leading to purine overproduction (rare monogenic disorders)
Hypoxanthine-guanine phosphoribosyltransferase deficiency
Phosphoribosylpyrophosphate synthetase overactivity
Glucose-6-phosphatase deficiency (glycogen storage disease, type I)
Clinical disorders leading to purine and/or urate overproduction
Myeloproliferative disorders
Lymphoproliferative disorders
Malignancies
Hemolytic disorders
Psoriasis
Obesity
Tissue hypoxia
Down syndrome
Glycogen storage diseases (types III, V, VII)
Drug-, diet-, or toxin-induced purine and/or urate overproduction
Ethanol
Excessive dietary purine ingestion
Pancreatic extract
Fructose
Vitamin B12 deficiency
Nicotinic acid
Ethylamino-1,3,4-thiadiazole
4-amino-5-imidazole carboxamide riboside
Cytotoxic drugs

UpToDate®

Up To Date: Feb. 2016

https://www.uptodate.com/contents/clinical-manifestations-and-diagnosis-of-gout?topicRef=514&source=see_link

Alcohol and Gout

- Risk of gout for various alcoholic beverages:
- Two or more beers/day = 2.5 fold increase risk.
- Two or more intake of spirits = 1.6 fold increased risk.
- Two 4 oz or more wine consumption was **not** associated with an increased risk of gout.
- These findings were independent of diet, age, BMI, hypertension or use of diuretics.

The Lancet: Alcohol intake and risk of incident gout in men: a prospective study. H Choi, K Atkinson, et al. Vol 363: April 17, 2004

Avoid Foods that Cause Gout

Gout commonly strikes between the ages of 30 and 50, usually occurring in men and, less often in women in menopause. Avoiding certain foods high in purine and keeping weight down are controllable risk factors.

Risky foods

Anchovies, herring/sardines

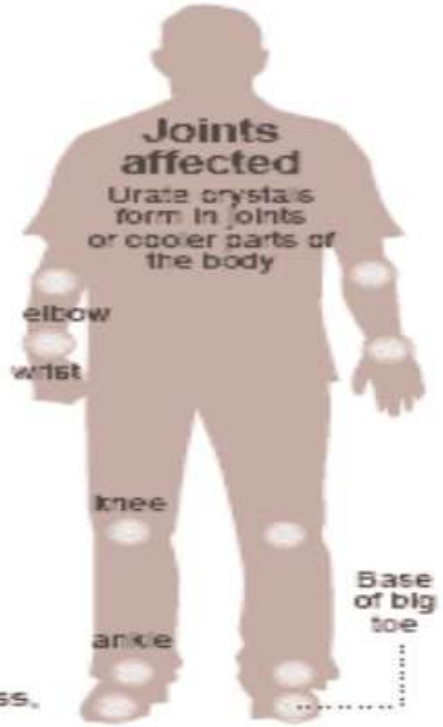
Mushrooms

Asparagus, peas and beans

Mussels

Kidney, liver, heart and brain, gravies, sweetbreads, broths and con-somme

Alcohol increases production of urate acid and interferes with elimination



Other risk factors include sudden severe illness, crash diets, joint injury and chemotherapy

Seafood	Meats	Vegetables
Anchovies	Liver	Asparagus
Codfish	Sweetbreads	Fava Beans
Haddock	Brains	Garbanzo Beans
Herring	Bacon	Edamame (soy)
Mackerel	Turkey	Mushrooms
Mussels	Veal	Peas
Sardines	Venison	Lentils
Scallops	Beef	Spinach
Trout	Chicken	Cauliflower
Crab	Duck	
Lobster	Ham	
Oysters	Pork	
Shrimp		

Purine-Rich Foods, Dairy and Protein Intake, and the Risk of Gout in Men

Hyon K. Choi, M.D., Dr.P.H., Karen Atkinson, M.D., M.P.H., Elizabeth W. Karlson, M.D., Walter Willett, M.D., Dr.P.H., and Gary Curhan, M.D., Sc.D.

- **12 year retrospective study.**
- 47,150 men with no h/o gout (> 40 years of age)
- Results
  - Additional weekly serving of purine rich red meat → **21% increase risk of gout**
  - Additional weekly serving of seafood → **7% increase risk of gout (particularly in low BMI patients).**

Table 3. Relative Risk of a New Case of Gout According to Intake of Purine-Rich Food Groups and Dairy Products.*

Variable	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Relative Risk per Additional Daily Serving
Total meat intake (servings/day)	<0.81	0.81–1.12	1.13–1.46	1.47–1.92	>1.92	
No. of cases/no. of person-yr	116/93,473	138/95,857	163/95,963	152/96,487	161/96,153	
Age-adjusted RR (95% CI)	1.0	1.20 (0.94–1.54)	1.48 (1.16–1.87)	1.51 (1.17–1.94)	1.77 (1.35–2.31)	1.37 (1.18–1.58)
Multivariate RR (95% CI)	1.0	1.07 (0.84–1.37)	1.28 (1.00–1.63)	1.26 (0.97–1.63)	1.41 (1.07–1.86)	1.21 (1.04–1.41)
Seafood intake (servings/day)	<0.15	0.15–0.28	0.29–0.36	0.37–0.56	>0.56	
No. of cases/no. of person-yr	71/64,193	171/120,274	163/97,175	154/94,868	171/101,423	
Age-adjusted RR (95% CI)	1.0	1.41 (1.10–1.81)	1.54 (1.21–1.98)	1.43 (1.11–1.85)	1.53 (1.20–1.96)	1.07 (1.02–1.12)†
Multivariate RR (95% CI)	1.0	1.35 (1.05–1.74)	1.45 (1.13–1.87)	1.38 (1.06–1.79)	1.51 (1.17–1.95)	1.07 (1.01–1.12)†
Purine-rich–vegetable intake (servings/day)	<0.35	0.35–0.50	0.51–0.71	0.72–1.05	>1.05	
No. of cases/no. of person-yr	137/92,144	147/92,919	150/93,165	163/102,976	133/96,729	
Age-adjusted RR (95% CI)	1.0	1.05 (0.83–1.32)	1.15 (0.91–1.45)	1.11 (0.87–1.40)	0.97 (0.75–1.24)	0.95 (0.78–1.16)
Multivariate RR (95% CI)	1.0	0.99 (0.79–1.25)	1.10 (0.87–1.40)	1.06 (0.84–1.36)	0.96 (0.74–1.24)	0.97 (0.79–1.19)
Total intake of dairy products (servings/day)	<0.88	0.88–1.35	1.36–1.91	1.92–2.88	>2.88	
No. of cases/no. of person-yr	201/94,123	165/93,040	132/98,103	130/97,729	102/94,937	
Age-adjusted RR (95% CI)	1.0	0.85 (0.69–1.04)	0.66 (0.53–0.83)	0.62 (0.49–0.78)	0.52 (0.40–0.67)	0.79 (0.73–0.86)
Multivariate RR (95% CI)	1.0	0.83 (0.68–1.03)	0.66 (0.53–0.83)	0.64 (0.51–0.82)	0.56 (0.42–0.74)	0.82 (0.75–0.90)
Intake of low-fat dairy products (servings/day)	<0.20	0.20–0.56	0.57–0.99	1.00–1.67	>1.67	
No. of cases/no. of person-yr	173/92,742	181/90,972	146/93,197	129/104,040	101/96,982	
Age-adjusted RR (95% CI)	1.0	1.06 (0.86–1.31)	0.83 (0.67–1.04)	0.67 (0.54–0.84)	0.56 (0.43–0.72)	0.76 (0.69–0.83)
Multivariate RR (95% CI)‡	1.0	1.01 (0.82–1.25)	0.80 (0.64–1.00)	0.67 (0.53–0.85)	0.58 (0.45–0.76)	0.79 (0.71–0.87)
Intake of high-fat dairy products (servings/day)	<0.34	0.34–0.63	0.64–0.99	1.00–1.64	>1.64	
No. of cases/no. of person-yr	142/94,708	161/93,886	144/94,448	141/99,037	142/95,853	
Age-adjusted RR (95% CI)	1.0	1.18 (0.94–1.47)	1.07 (0.85–1.35)	1.03 (0.81–1.30)	1.10 (0.86–1.41)	1.01 (0.91–1.11)
Multivariate RR (95% CI)‡	1.0	1.09 (0.87–1.37)	0.98 (0.77–1.25)	0.92 (0.72–1.18)	1.00 (0.77–1.29)	0.99 (0.89–1.10)

* RR denotes relative risk, and CI confidence interval. The age-adjusted models were adjusted for the total energy intake as well as age; the multivariate models were adjusted for age, total energy intake, body-mass index, use of diuretics, presence or absence of a history of hypertension, presence or absence of a history of renal failure, and intake of alcohol, fluid, total meats, seafood, purine-rich vegetables, and dairy products.
† In order to reflect the distribution of seafood intake, the data represent the relative risk per additional weekly serving.
‡ The multivariate model included the intake of low-fat dairy products and high-fat dairy products instead of that of total dairy products.

N Engl J Med 2004; 350:1093-1103.

- During 12 years of the study 730 confirmed new cases of gout.
- 88% of men reported podagra, with 35% demonstrating midfoot involvement.
- Other Findings
  - Intake of low fat dairy as well as purine rich vegetable protein may be protective.

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N Engl J Med 2004; 350:1093-1103.

INDUCERS OF ACUTE ATTACK

- Trauma
- Surgery
- Diet
- Changes in EtOH intake
- Changes in Medications
- Dehydration 

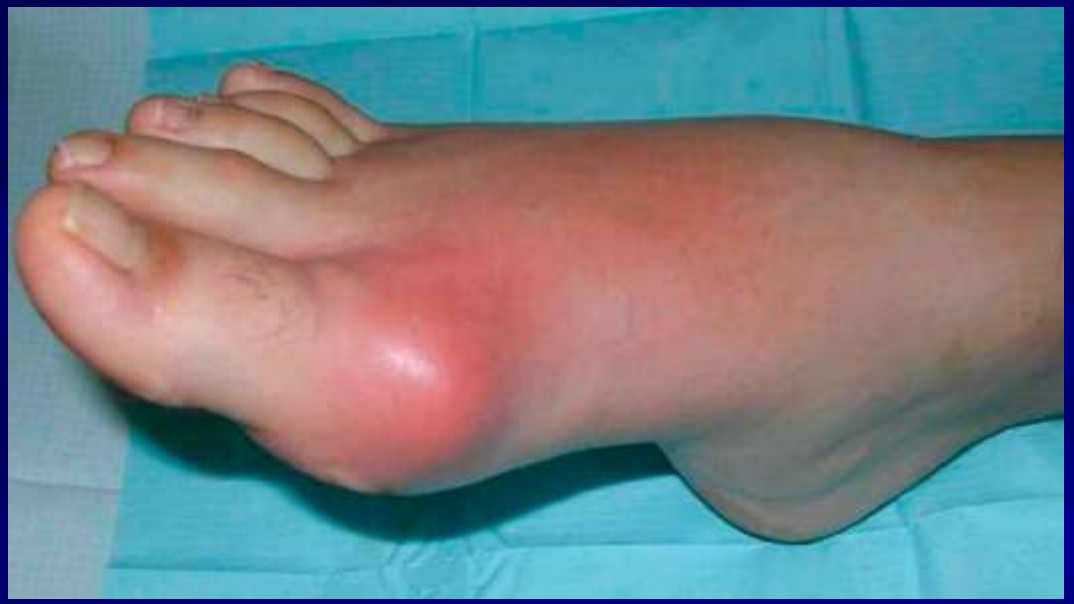
Diagnosis of Gout

- Gout (monosodium urate [MSU] crystal deposition disease) is characterized biochemically by extracellular fluid urate saturation, which is reflected in the blood by hyperuricemia, with serum or plasma urate concentrations exceeding 6.8 mg/dL (approximately 400 micromol/L); this level of urate is the approximate limit of urate solubility.

- ACR Guidelines (2012) recommend the goal of Gout management is to achieve < 6.0 mg/dL

UptoDate.com/clinical manifestations and diagnosis of Gout: Feb. 2018

Clinical Presentation



- **Red, Hot, Swollen!**
- First Metatarsal Phalangeal Joint
- Pain started at night

- “I can’t even let the sheets touch my foot”

pathogenesis

Hyperuricaemia

⇩

May be asymptomatic

⇩

Deposition of monosodium urate crystals in synovial tissue
(contain various Ig's, complement, fibrinogen, fibronectin)

⇩

Complement activated

⇩

Neutrophils phagocytose & lyse crystals

⇩

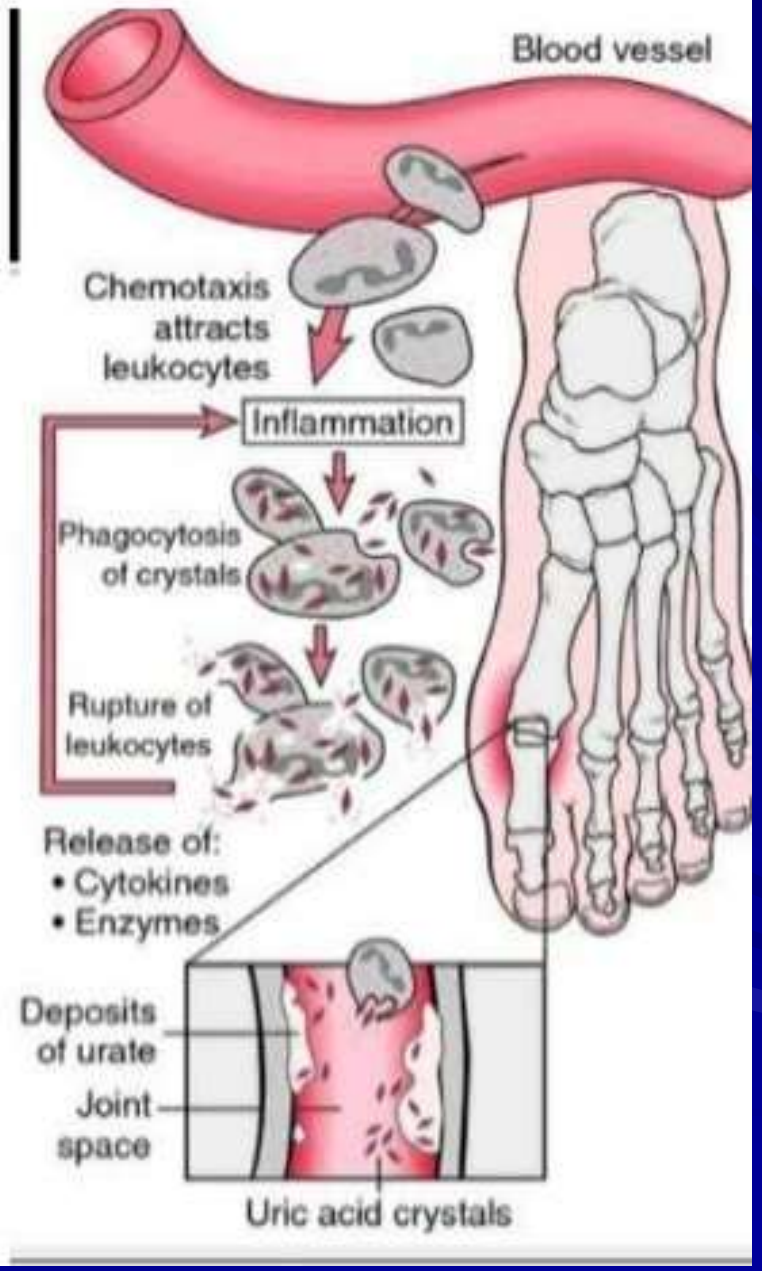
Release chemical mediators (e.g. TNF-α; IL-1)

⇩

ACUTE GOUTY ARTHRITIS

⇩

May resolve & become asymptomatic
(INTERCRITICAL GOUT)



ARTHRITIS & RHEUMATOLOGY
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DOI 10.1002/art.38917

Nocturnal Risk of Gout Attacks

Hyon K. Choi,[1] Jingbo Niu,[1] Tuhina Neogi,[1] Clara A. Chen,[1] Christine Chaisson,[1] David Hunter,[2] and Yuqing Zhang[1]

Objective. **Several plausible mechanisms and anecdotal descriptions suggest that gout attacks often occur at night, although there are no scientific data supporting this. We undertook this study to evaluate the hypothesis that gout attacks occur more frequently at night.**

Methods. **We conducted a case-crossover study to examine the risk of acute gout attacks in relation to the time of the day. Gout patients were prospectively recruited and followed up via the internet for 1 year. Participants were asked about the following information concerning their gout attacks: the date and hour of attack onset, symptoms and signs, medication use, and purported risk factors during the 24- and 48-hour periods prior to the gout attack. We calculated the odds ratios (ORs) of gout attacks (with 95% confidence intervals [95% CIs]) according to three 8-hour time blocks of the day (i.e., 12:00 AM to 7:59 AM, 8:00 AM to 3:59 PM [reference], and 4:00 PM to 11:59 PM) using conditional logistic regression.**

Results. **Our study included 724 gout patients who experienced a total of 1,433 attacks (733, 310, and 390 attacks during the first, second, and third 8-hour time blocks, respectively) over 1 year. The risk of gout flares in the 8-hour overnight time block (12:00 AM to 7:59 AM) was 2.36 times higher than in the daytime (8:00 AM to 3:59 PM) (OR 2.36 [95% CI 2.05–2.73]). The corresponding OR in the evening (4:00 PM to 11:59 PM) was 1.26 (95% CI 1.07–1.48). These associations persisted among those with no alcohol use and in the lowest quintile of purine intake in the 24 hours prior to attack onset. Furthermore, these associations persisted in subgroups according to sex, age group, obesity status, diuretic use, and use of allopurinol, colchicine, and nonsteroidal antiinflammatory drugs.**

Conclusion. **These findings provide the first prospective evidence that the risk of gout attacks during the night and early morning is 2.4 times higher than in the daytime. Further, these data support the purported mechanisms and historical descriptions of the nocturnal onset of gout attacks and may have implications for antigout prophylactic measures.**

Gout is the most common inflammatory arthritis in the US (1–3), and acute gout flares are among the most painful events experienced by humans (4). Several plausible mechanisms and historical and anecdotal descriptions suggest that gout attacks often occur at night; however, no scientific data are available. For example, Thomas Sydenham, the famous 17th century physician, wrote of his personal experiences with gout: "He goes to bed and sleeps well, but about Two a Clock in the Morning, is waked by the Pain, seizing either his great Toe, the Heel, the Calf of the Leg, or the Ankle; this pain is like that of dislocated Bones . . . the Part affected has such a quick and exquisite Pain, that is not able to bear the weight of the cloths upon it, nor hard walking in the Chamber" (5).

It has been speculated that lower body temperature, relative nocturnal dehydration, or the nocturnal dip in cortisol levels may lead to an increased risk of gout attacks at night. Another hypothesis for the typical nocturnal onset is the potential role of sleep apnea (6,7), which is common among obese men with multiple comorbidities, a typical profile of gout patients. Hyponia

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Dr. Choi has received consulting fees, speaking fees, and/or honoraria from AstraZeneca and Takeda (less than $10,000 each) and research funding from AstraZeneca.

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It Woke me up!

- **Conclusion. These findings provide the first prospective evidence that the risk of gout attacks during the night and early morning is 2.4 times higher than in the daytime.**
- **Further, these data support the purported mechanisms and historical descriptions of the nocturnal onset of gout attacks and may have implications for antigout prophylactic measures.**

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Nocturnal Risk of Gout Attacks

Hyon K. Choi,[1] Jingbo Niu,[1] Tuhina Neogi,[1] Clara A. Chen,[1] Christine Chaisson,[1] David Hunter,[2] and Yuqing Zhang[1]

Objective. Several plausible mechanisms and anecdotal descriptions suggest that gout attacks often occur at night, although there are no scientific data supporting this. We undertook this study to evaluate the hypothesis that gout attacks occur more frequently at night.

Methods. We conducted a case-crossover study to examine the risk of acute gout attacks in relation to the time of the day. Gout patients were prospectively recruited and followed up via the internet for 1 year. Participants were asked about the following information concerning their gout attacks: the date and hour of attack onset, symptoms and signs, medication use, and purported risk factors during the 24- and 48-hour periods prior to the gout attack. We calculated the odds ratios (ORs) of gout attacks (with 95% confidence intervals [95% CIs]) according to three 8-hour time blocks of the day (i.e., 12:00 AM to 7:59 AM, 8:00 AM to 3:59 PM [reference], and 4:00 PM to 11:59 PM) using conditional logistic regression.

Results. Our study included 724 gout patients who experienced a total of 1,433 attacks (733, 310, and 390 attacks during the first, second, and third 8-hour time blocks, respectively) over 1 year. The risk of gout flares in the 8-hour overnight time block (12:00 AM to 7:59 AM) was 2.36 times higher than in the daytime (8:00 AM to 3:59 PM) (OR 2.36 [95% CI 2.05–2.73]). The corresponding OR in the evening (4:00 PM to 11:59 PM) was 1.26 (95% CI 1.07–1.48). These associations persisted among those with no alcohol use and in the lowest quintile of purine intake in the 24 hours prior to attack onset. Furthermore, these associations persisted in subgroups according to sex, age group, obesity status, diuretic use, and use of allopurinol, colchicine, and nonsteroidal antiinflammatory drugs.

Conclusion. These findings provide the first prospective evidence that the risk of gout attacks during the night and early morning is 2.4 times higher than in the daytime. Further, these data support the purported mechanisms and historical descriptions of the nocturnal onset of gout attacks and may have implications for antigout prophylactic measures.

Gout is the most common inflammatory arthritis in the US (1–3), and acute gout flares are among the most painful events experienced by humans (4). Several plausible mechanisms and historical and anecdotal descriptions suggest that gout attacks often occur at night; however, no scientific data are available. For example, Thomas Sydenham, the famous 17th century physician, wrote of his personal experiences with gout: "He goes to bed and sleeps well, but about Two a Clock in the Morning, is waked by the Pain, seizing either his great Toe, the Heel, the Calf of the Leg, or the Ankle; this pain is like that of dislocated Bones . . . the Part affected has such a quick and exquisite Pain, that is not able to bear the weight of the cloths upon it, nor hard walking in the Chamber" (5).

It has been speculated that lower body temperature, relative nocturnal dehydration, or the nocturnal dip in cortisol levels may lead to an increased risk of gout attacks at night. Another hypothesis for the typical nocturnal onset is the potential role of sleep apnea (6,7), which is common among obese men with multiple comorbidities, a typical profile of gout patients. Hypoxia

Supported by the Arthritis Foundation, the Rheumatology Research Foundation, and the NIH (grant AR-47785).

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Why ?

- Diurnal variations in body temperature ranges from 37.5° C between 10am and 6pm to 36.4° C between 2am and 6am leading to a higher risk if UA crystallization.
- Relative dehydration
- Diurnal variations of blood cortisol levels.
- Sleep Apnea

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- **Sleep apnea – hypoxia can enhance nucleotide turnover, thereby generating purines.**
- **Up to 50% of sleep apnea patients have been found to have hyperuricemia.**

Hasday JD, Grum CM. Nocturnal increase of urinary uric acid: creatinine ratio: a biochemical correlate of sleep-associated hypoxemia. Am Rev Respir Dis 1987;135:534–8.

Roddy et al. BMC Musculoskeletal Disorders 2013, 14:119
http://www.biomedcentral.com/1471-2474/14/119

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

The association of gout with sleep disorders: a cross-sectional study in primary care

Edward Roddy*†, Sara Muller†, Richard Hayward† and Christian D Mallen†

Abstract

Background: Both gout and sleep apnoea are associated with the metabolic syndrome. Hyperuricaemia is also prevalent in sleep apnoea syndrome. The objective of this study was to examine the association between gout and sleep apnoea and other sleep disorders.

Methods: Data were taken from a validated database of general practice records from nine practices in the UK between 2001 and 2008. People consulting for gout were identified via Read codes and each matched with four controls for age, gender, practice and year of gout consultation. Sleep problems and confounding comorbidities were also identified via Read codes. Medications were identified through a linked database of prescription records. The association between gout and sleep disorders was assessed using a logistic regression model, adjusting for ischaemic heart disease, hypertension, diabetes mellitus and diuretic use.

Results: 1689 individuals with gout were identified and each successfully matched to four controls. Amongst those with gout, the prevalence of any sleep problem was 4.9%, sleep problems other than sleep apnoea 4.2%, and sleep apnoea 0.7%, compared to 3.5%, 3.2% and 0.3% respectively in controls. Gout was associated with any sleep problem (odds ratio (OR) 1.44; 95% confidence interval (CI) 1.11, 1.87), sleep problems other than sleep apnoea (OR 1.36; 95% CI 1.03, 1.80), and sleep apnoea (OR 2.10; 95% CI 1.01, 4.39). On multivariable analysis, gout remained significantly associated with any sleep problem (OR 1.39; 95% CI 1.06, 1.81) and sleep problems other than sleep apnoea (OR 1.37; 95% CI 1.03, 1.82), however the association with sleep apnoea was attenuated (OR 1.48, 95% CI 0.70, 3.14).

Conclusions: Gout and sleep problems appear to be associated and clinicians should be aware of the co-existence of these two conditions. Larger prospective epidemiological studies are required to explore causality.

Keywords: Gout, Sleep, Apnea, General practice, Metabolic syndrome X

Background

Gout is the most prevalent inflammatory arthropathy and affects approximately 1.4% of adults [1,2]. It is associated with considerable co-morbidity. The metabolic syndrome is present in over 60% of individuals with gout, who are more than three times more likely to have the metabolic syndrome than control subjects without gout [3]. Individual components of the metabolic syndrome such as hypertension, obesity and diabetes mellitus are recognised to be independent risk factors for the development of gout [4]. Insulin resistance is thought to be the major mediator of hyperuricaemia, the primary risk factor for the development of gout, in the metabolic syndrome [5] although hypertension exerts renal vascular effects which also predispose to hyperuricaemia [6]. Perhaps, not surprisingly, given its association with traditional cardiovascular risk factors, gout is associated with a considerable burden of cardiovascular disease. However, recent prospective epidemiological studies have suggested that gout confers additional independent cardiovascular risk after adjustment for traditional risk factors [7-10].

Obstructive sleep apnoea syndrome is also a common problem in primary care having a similar prevalence to gout of approximately 1–4% [11,12], although there is evidence that it is under-diagnosed in this setting [13,14]. Similar to gout, obstructive sleep apnoea syndrome is

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Conclusions:

Our findings support an association between gout and sleep disorders, although the association with obstructive sleep apnea syndrome does not appear to be independent of co-morbid confounding factors.

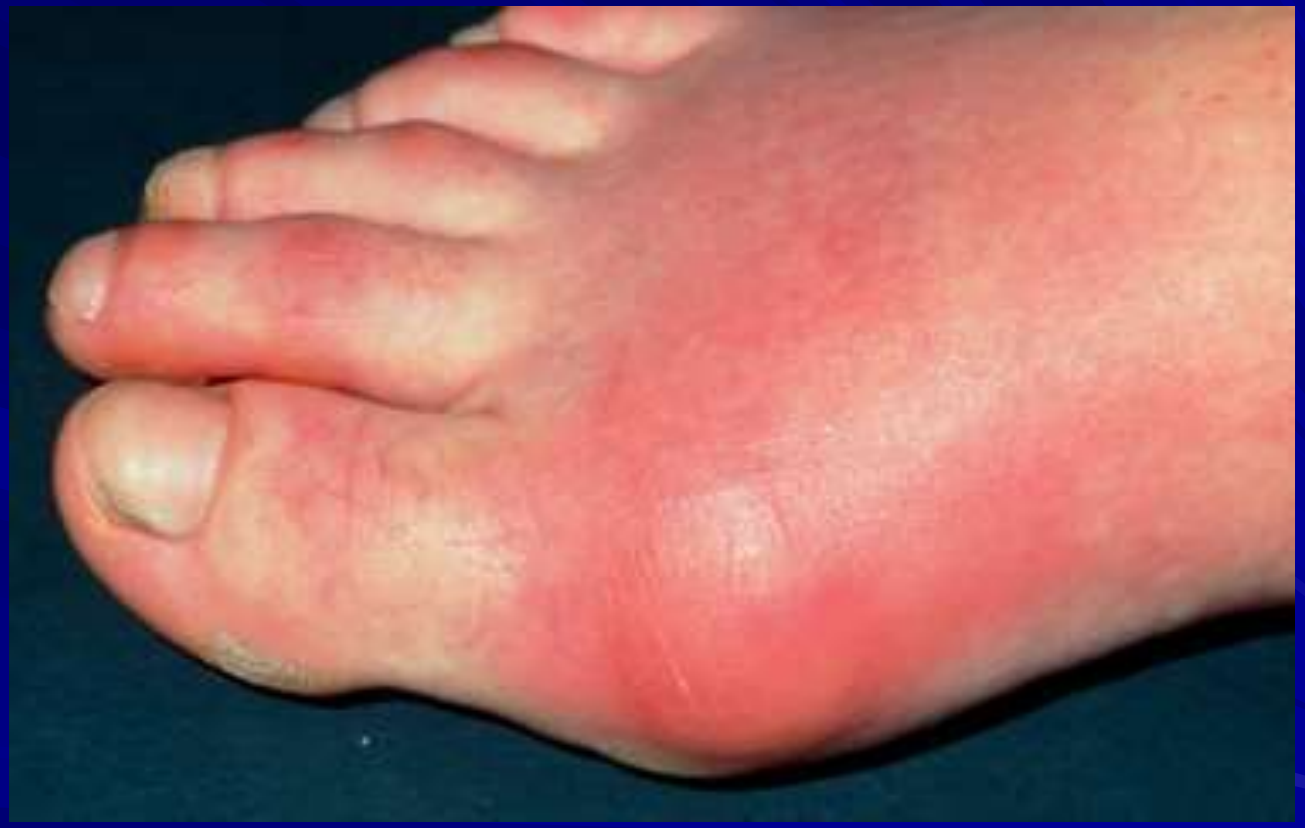
However, the potential co-existence of these two common conditions is an important message for clinicians and deserves wider recognition.

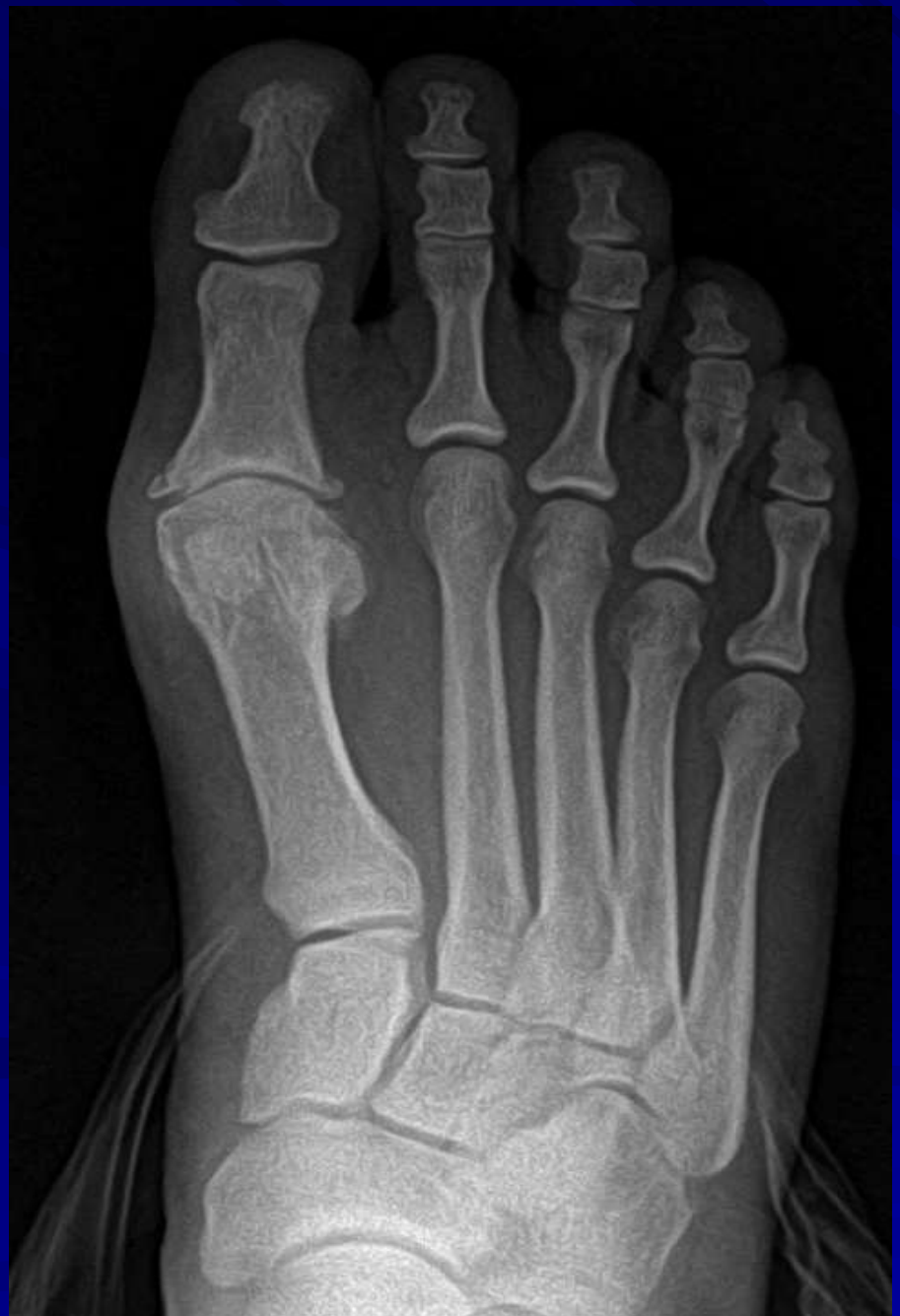
Future studies should focus on establishing the independence of this association and causality and examine whether treatment strategies benefit both conditions.

Roddy E, Muller S, Hayward R, Mallen CD. The association of gout with sleep disorders: a cross-sectional study in primary care. BMC Musculoskelet Disord 2013;14:119.

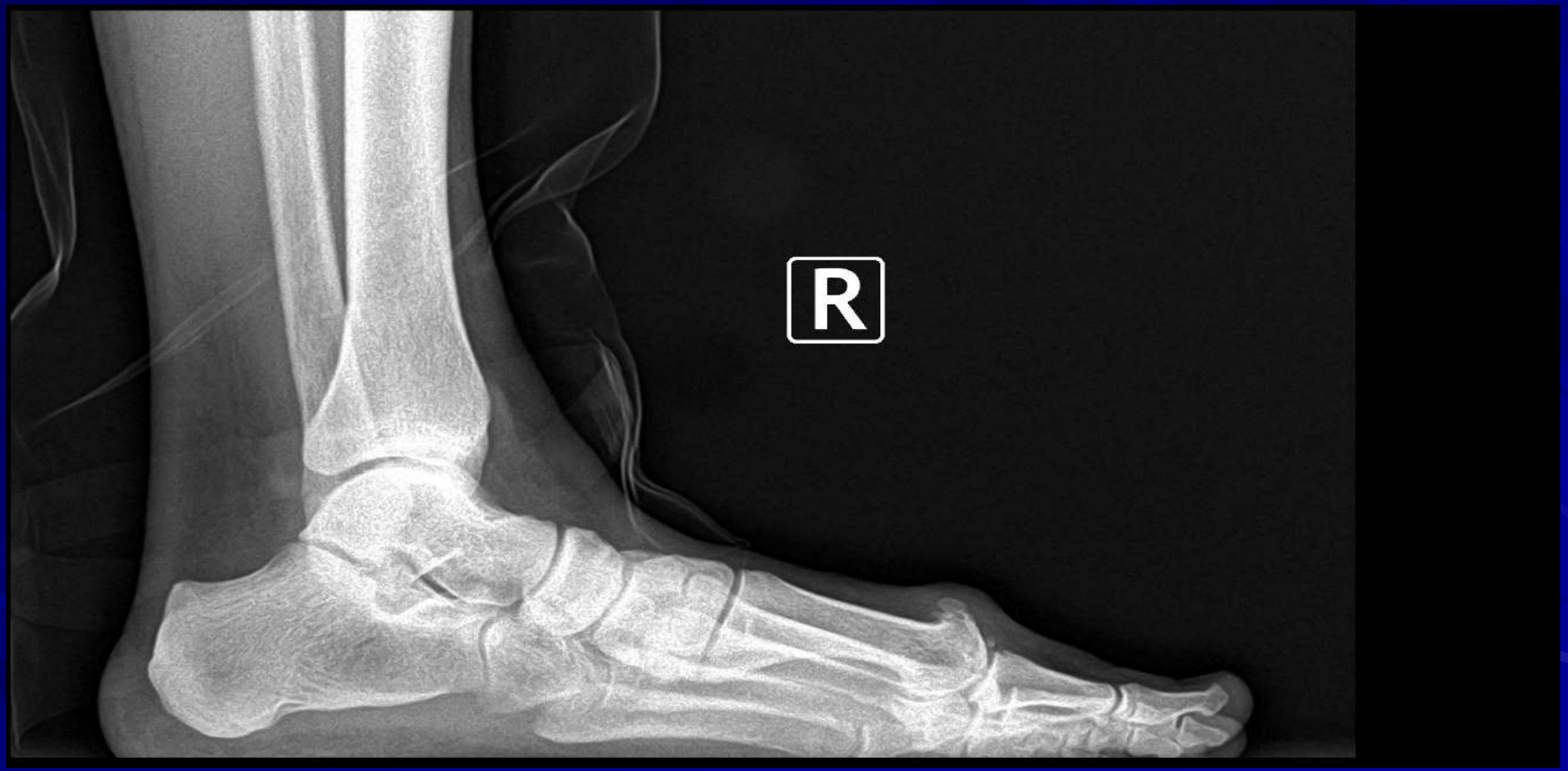
Differential Diagnosis

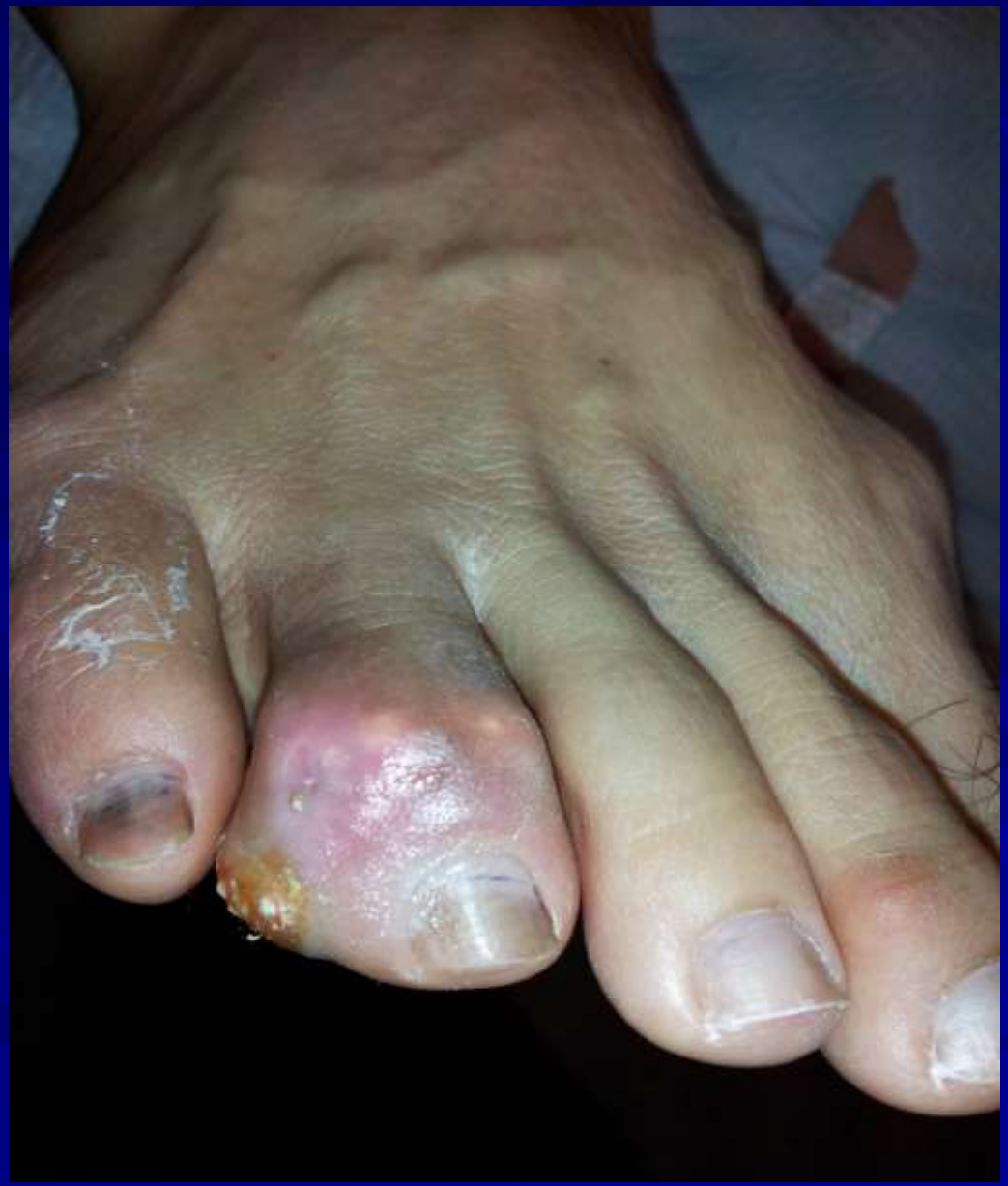
- Gout
- Septic Joint
- Trauma

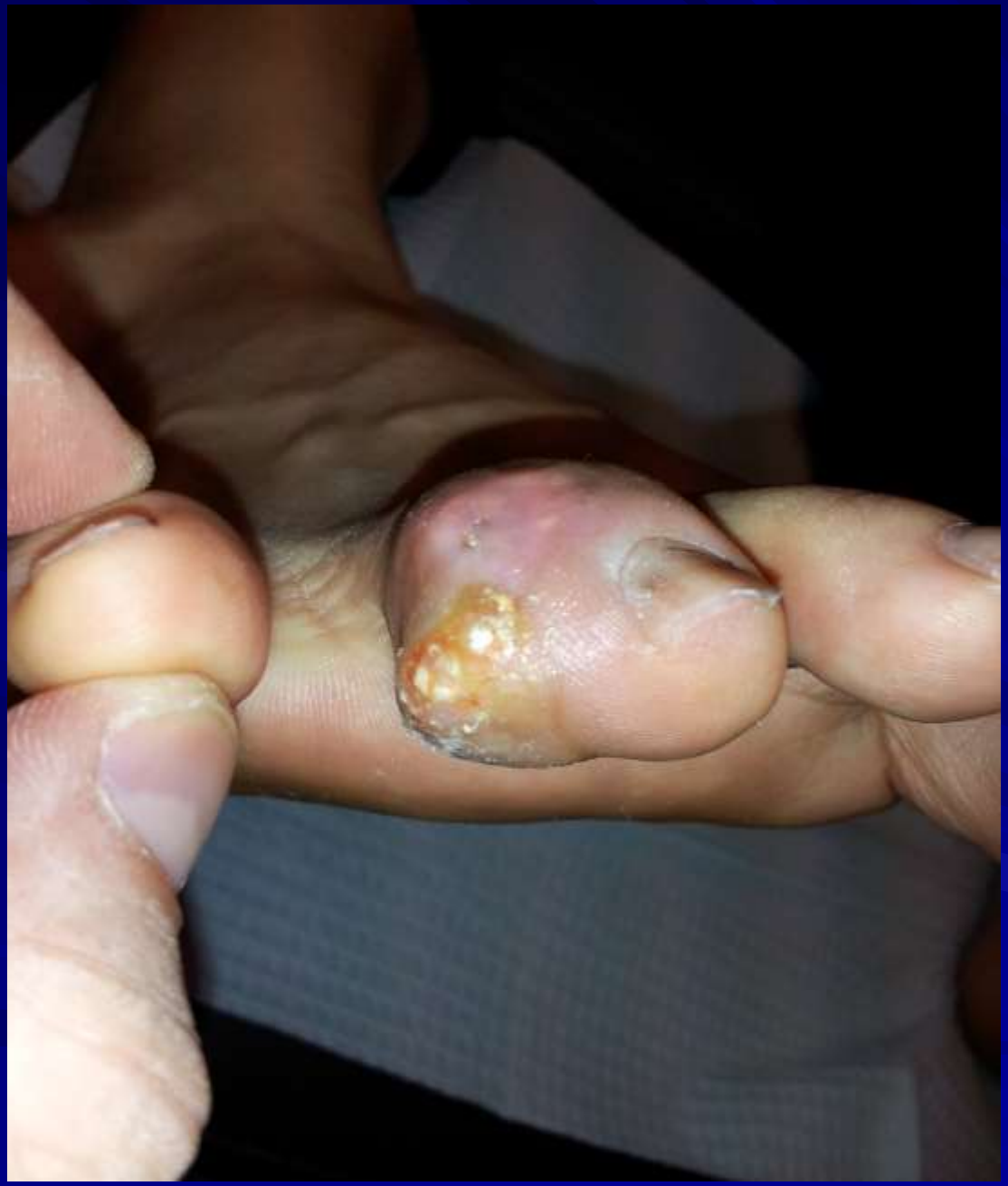


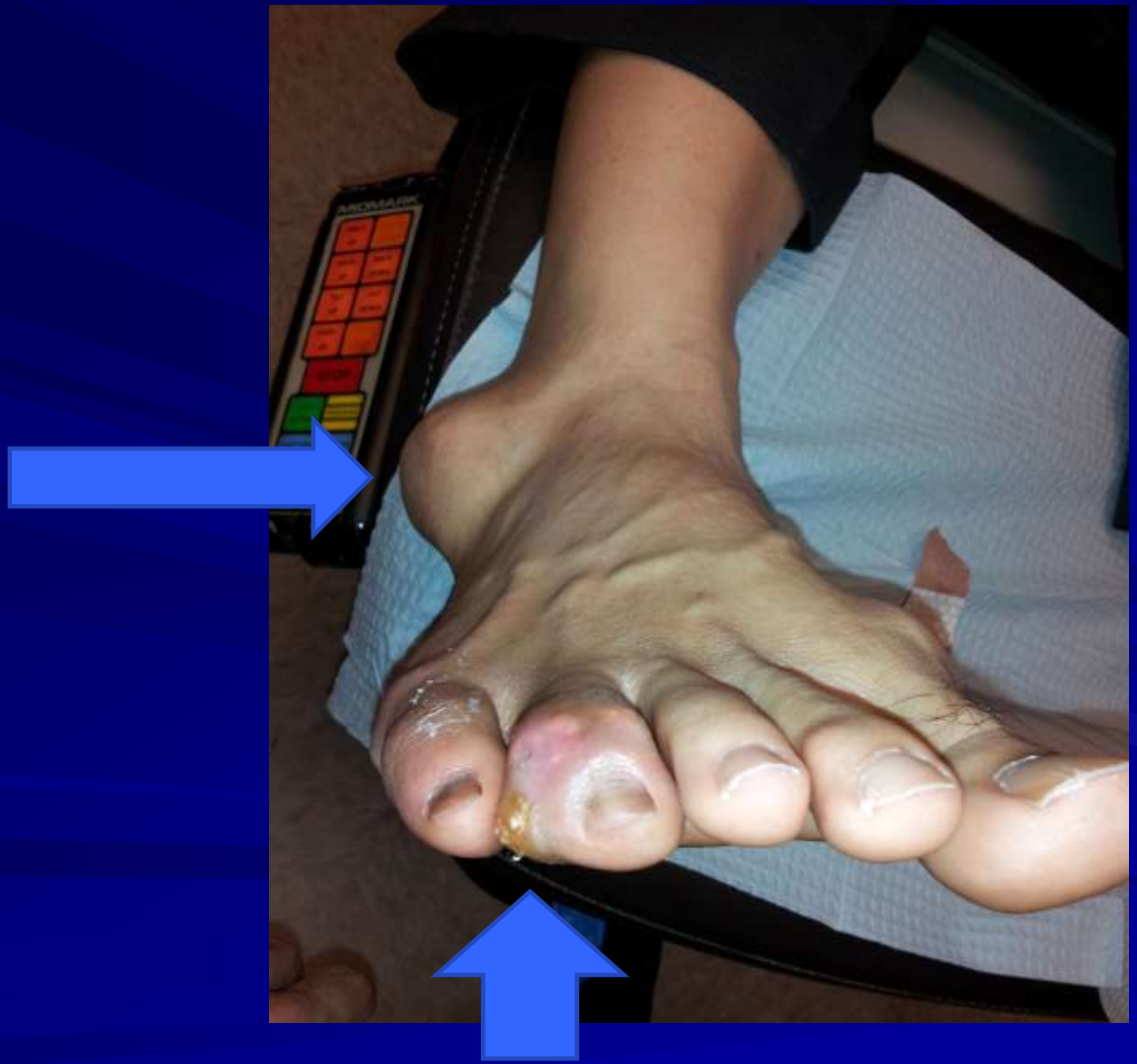


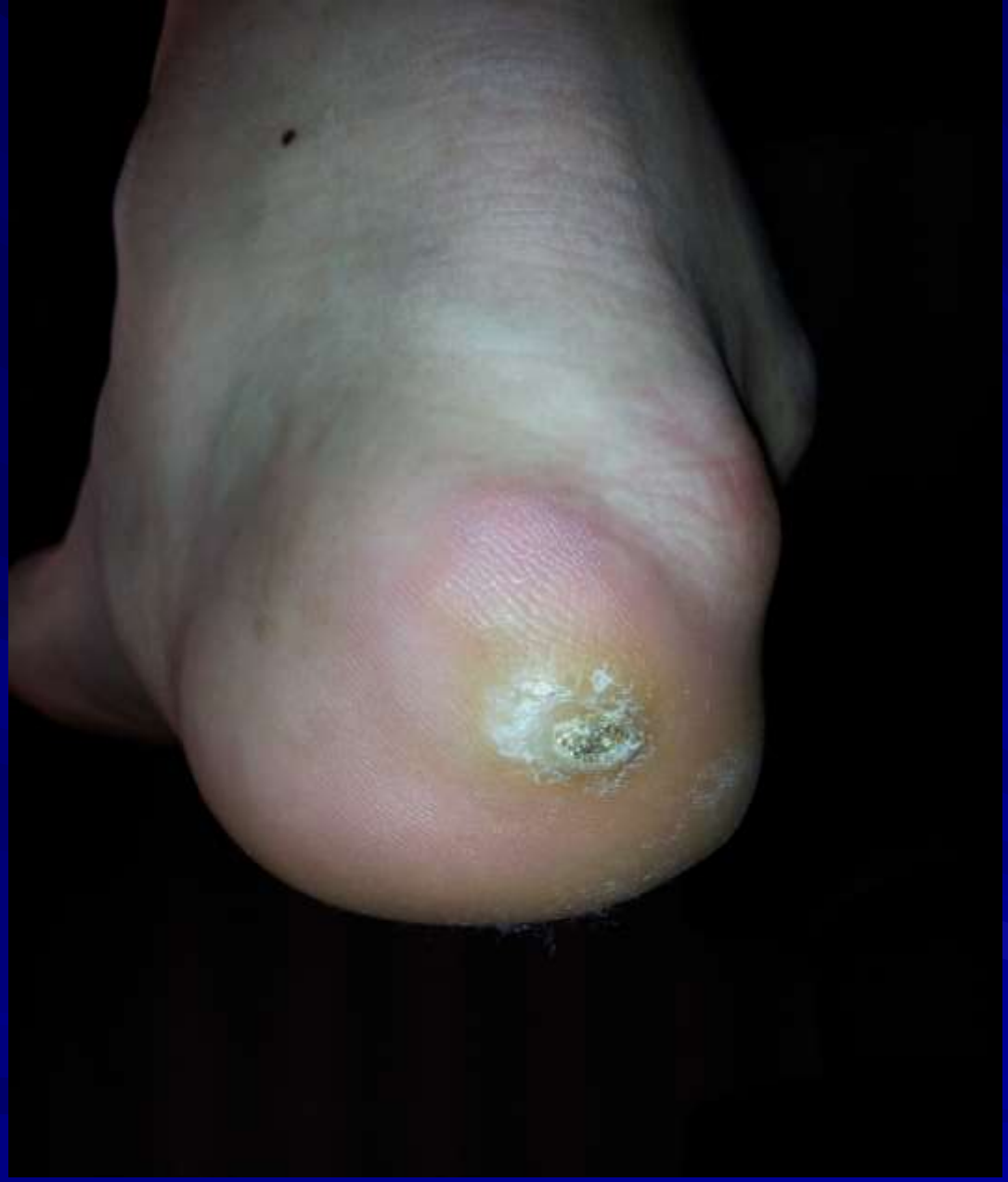
Imaging









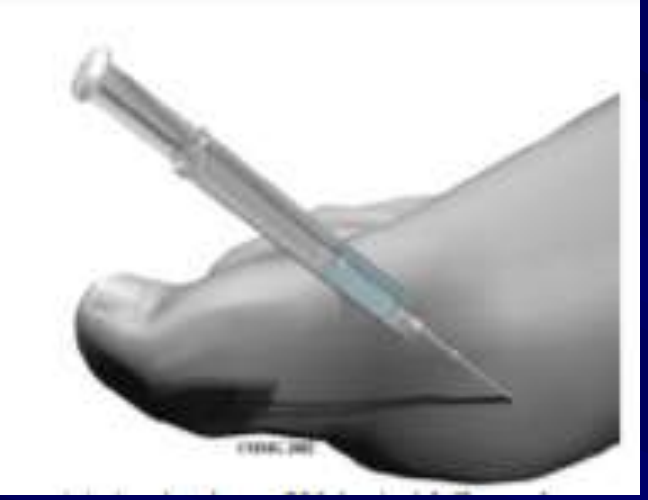


Courtesy: Leland Jaffe, DPM, North Chicago, IL

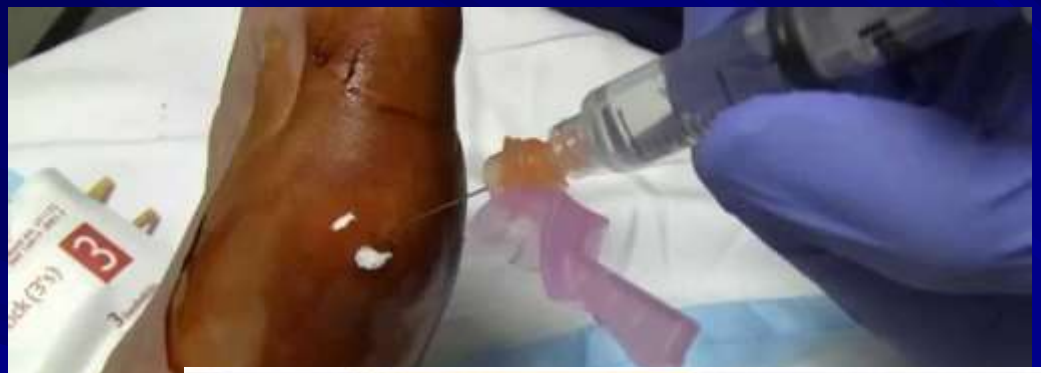
Definitive Diag. via Jt. Aspiration

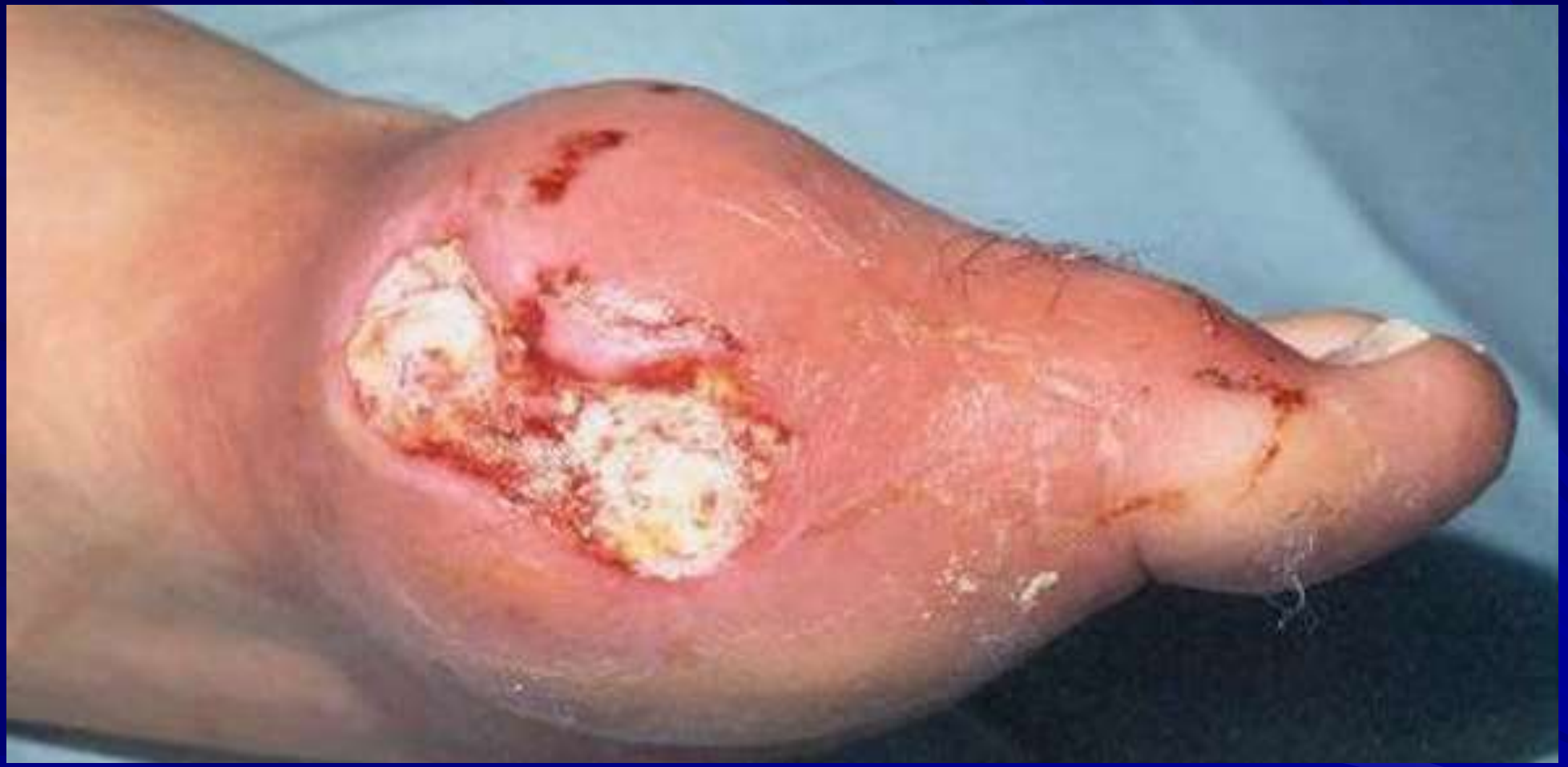
- But – Isn't this more commonly a "Clinical Diagnosis?
- How commonly do you aspirate the joint?
  - **Always** (100%)
  - **Mostly** (75%)
  - **Commonly** (50%)
  - **Rarely** (25%)
  - **Never** (0%)

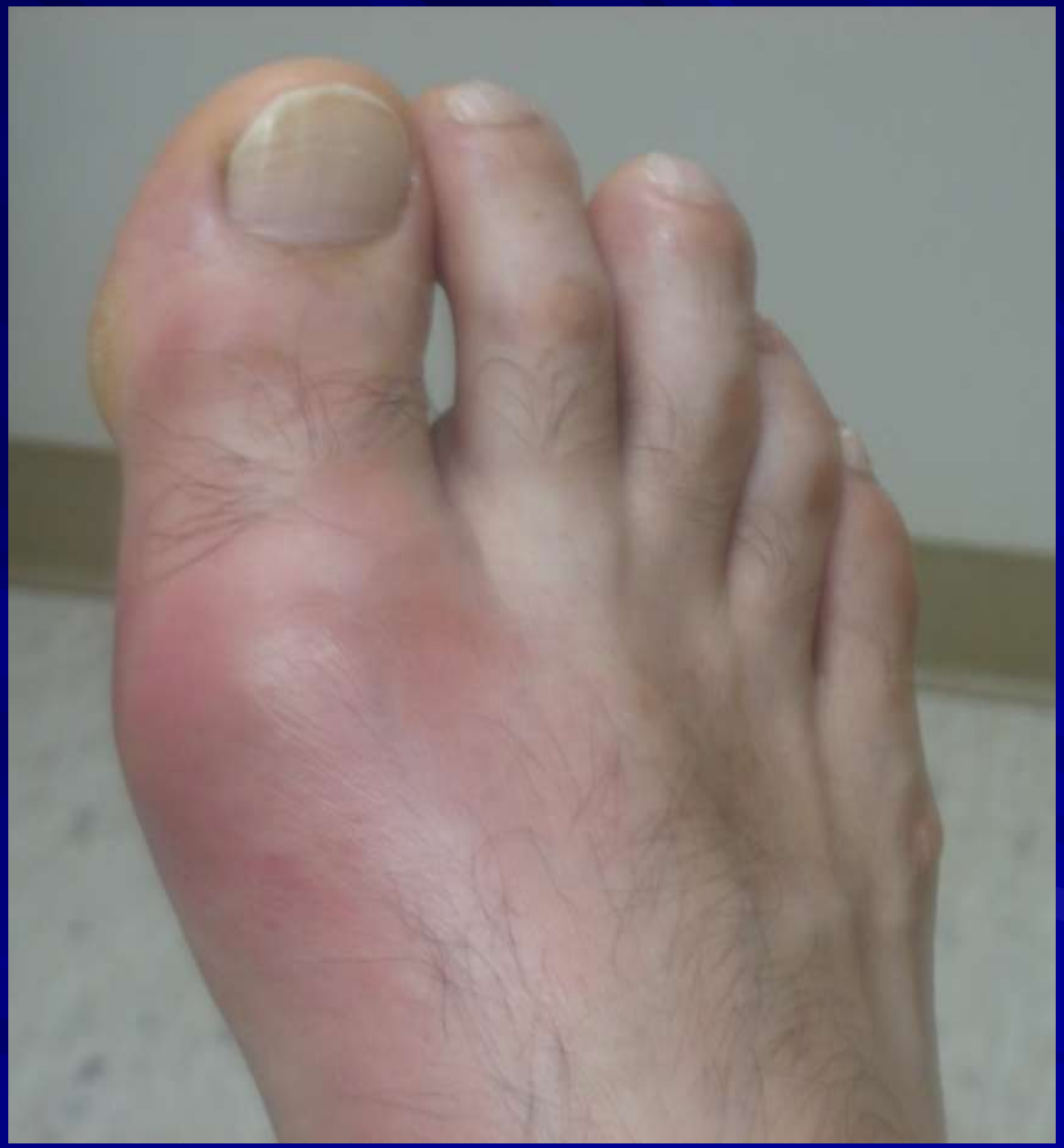
INFORMAL POLL



I'd Tap That!







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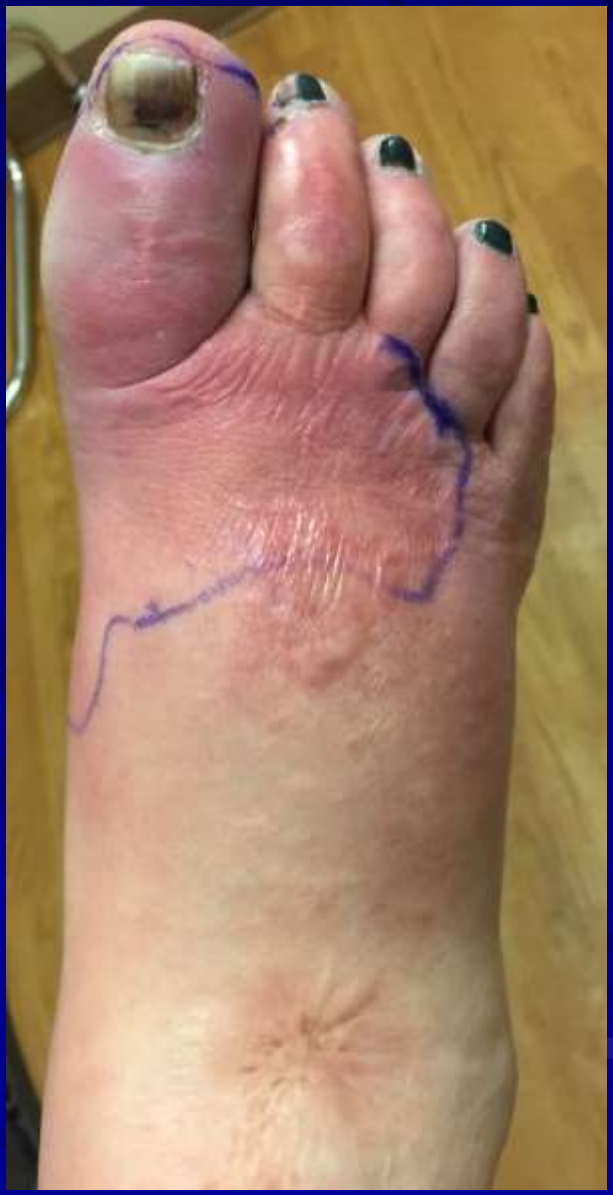


Courtesy Gina Painter, DPM Great Falls, MT

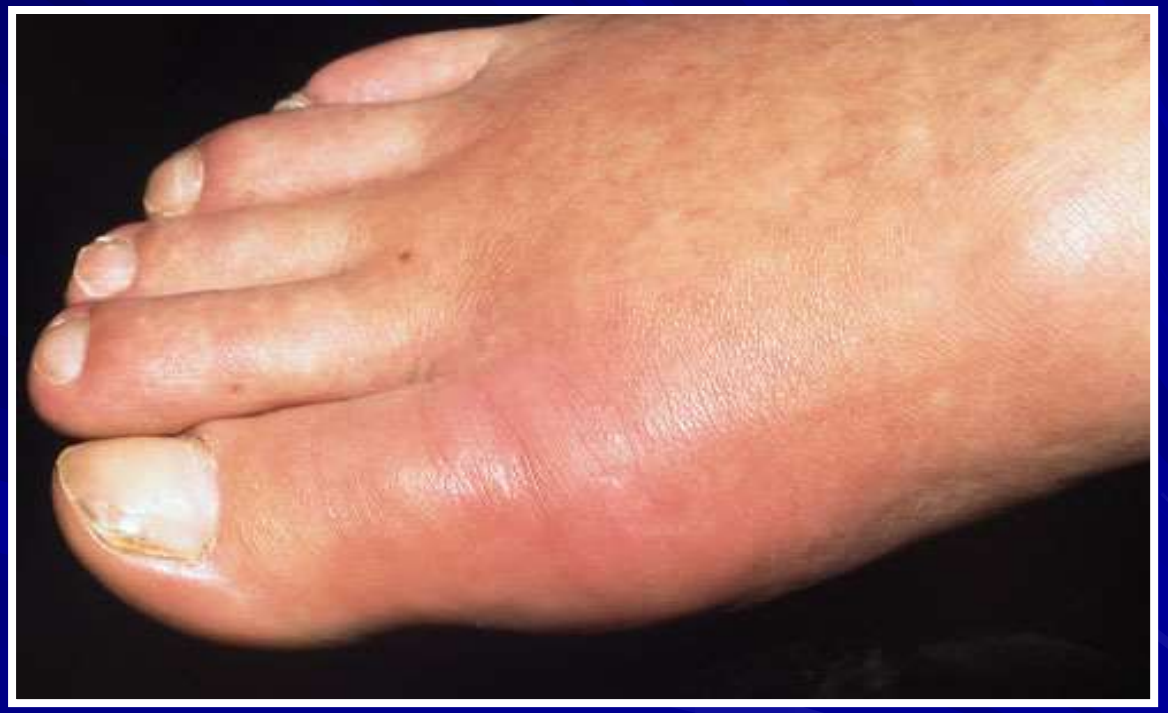
“Reductio Ad Absurdum”

Jarrod Shapiro, DPM
Practice Perfect Editor
Associate Professor
Dept. of Podiatric Medicine
Surgery & Biomechanics
College of Podiatric Medicine
Western University of
Health Sciences
Pomona, CA

- “Reduction to Absurdity”
- History & Clinical Exam
  - Labs
  - Radiographs
  - Ultrasound
  - MRI
  - DECT

Gouty Arthritis

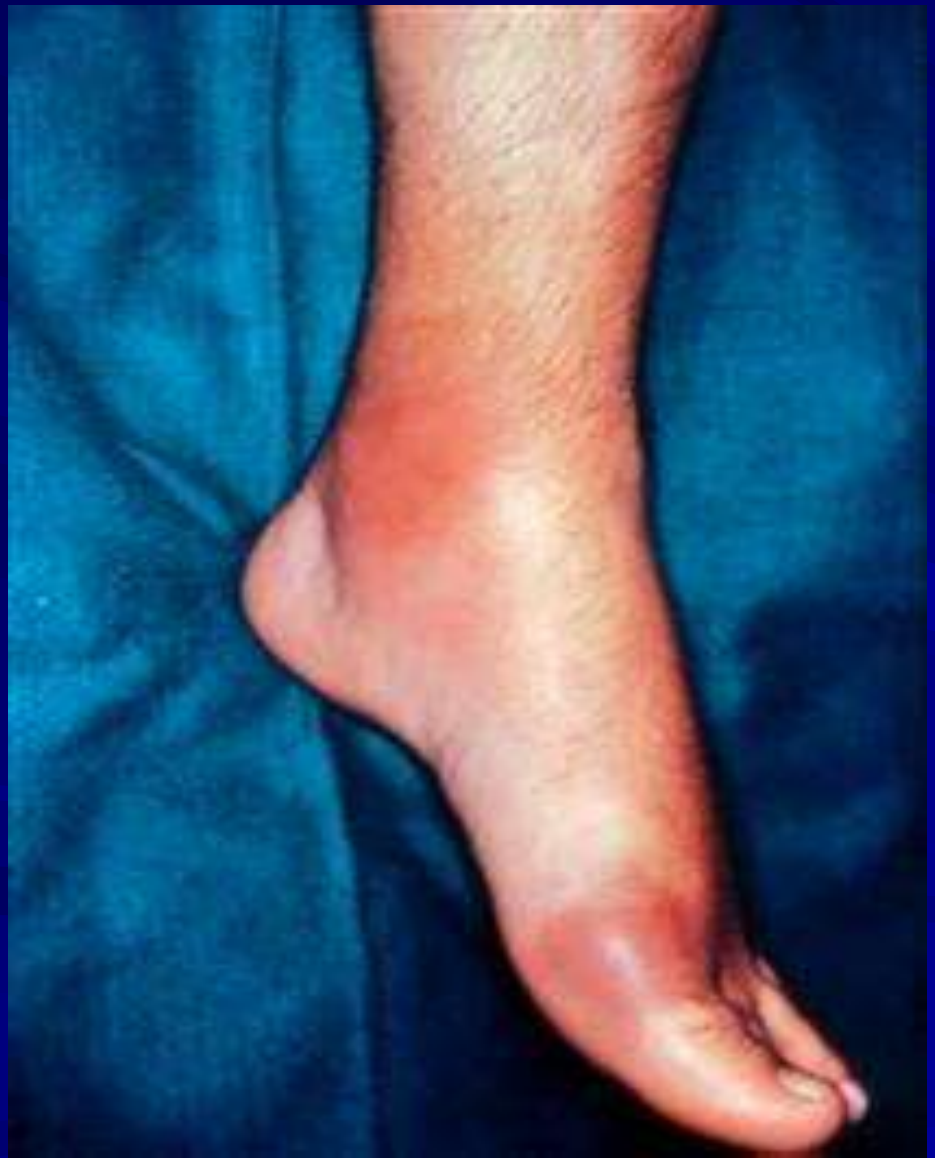
- **Acute Monoarticular Gout (3-10 days)**
  - **Quick onset**
  - **Severe crushing pain**
  - **Affected joint (usually 1st MPJ) edematous, hot and dry**
  - **10% will never experience another attack**
  - **60% experience a second attack within a year**



Red, hot, swollen joint, so why isn't Gout considered an Inflammatory Arthritide?

*Inflammation is short-lived (7-10days)

Gouty Arthritis

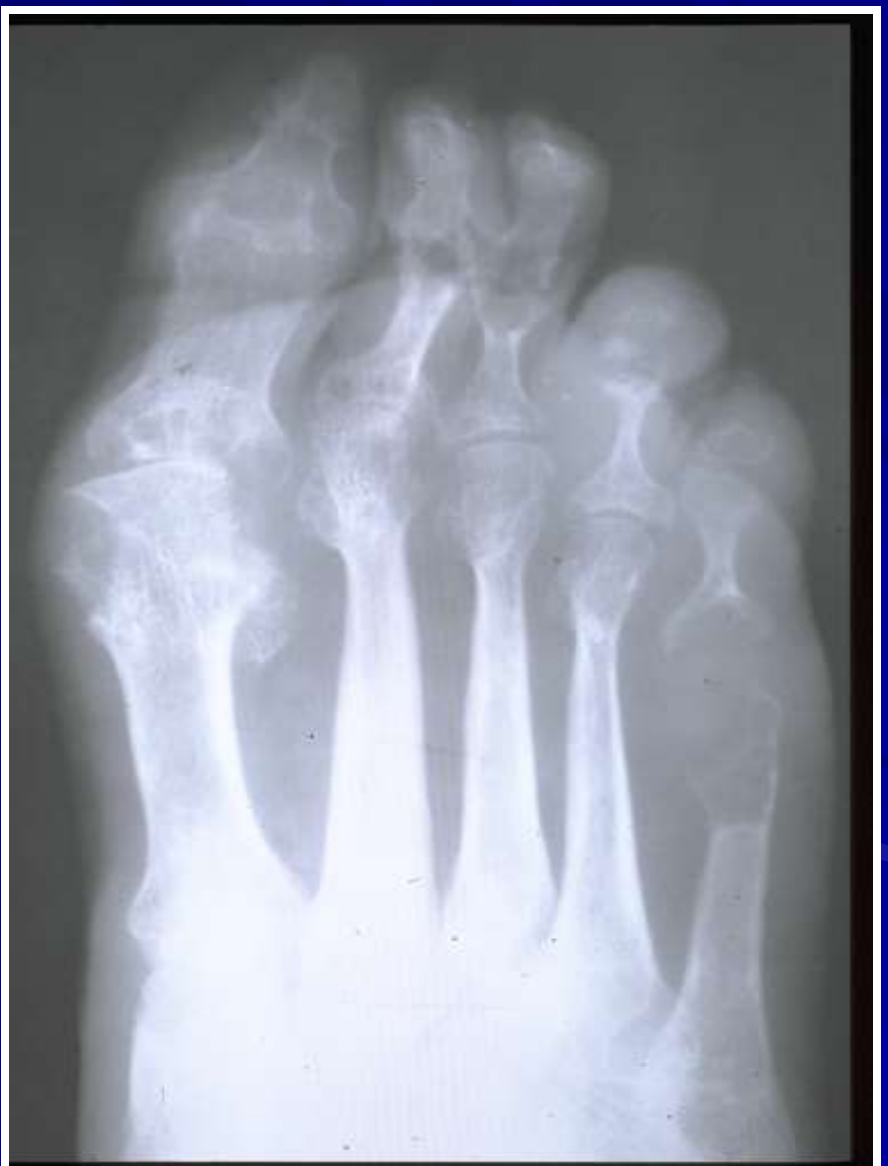


- **Polyarticular Gout**
  - Recurrent attacks may or may not affect joint initially involved
  - Attacks less severe but prolonged
  - X-ray changes in 33% of patients

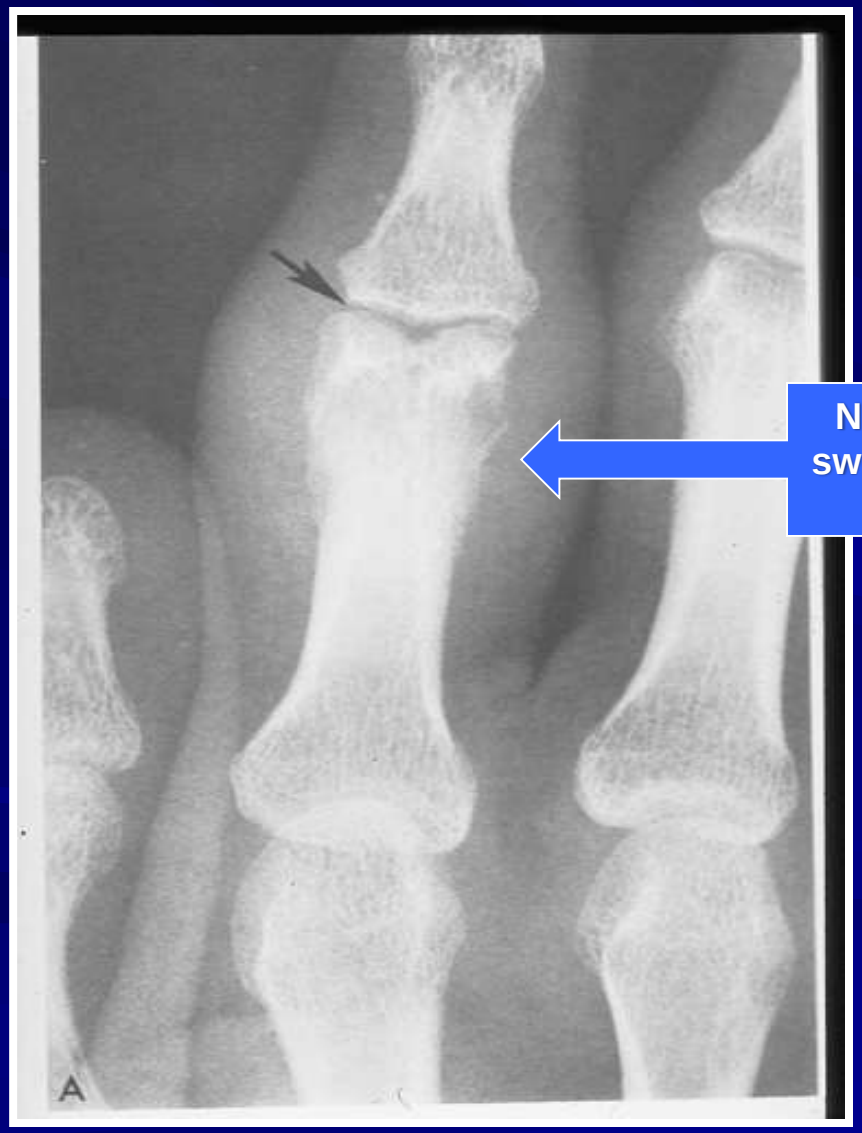
Gouty Arthritis

Chronic Gout

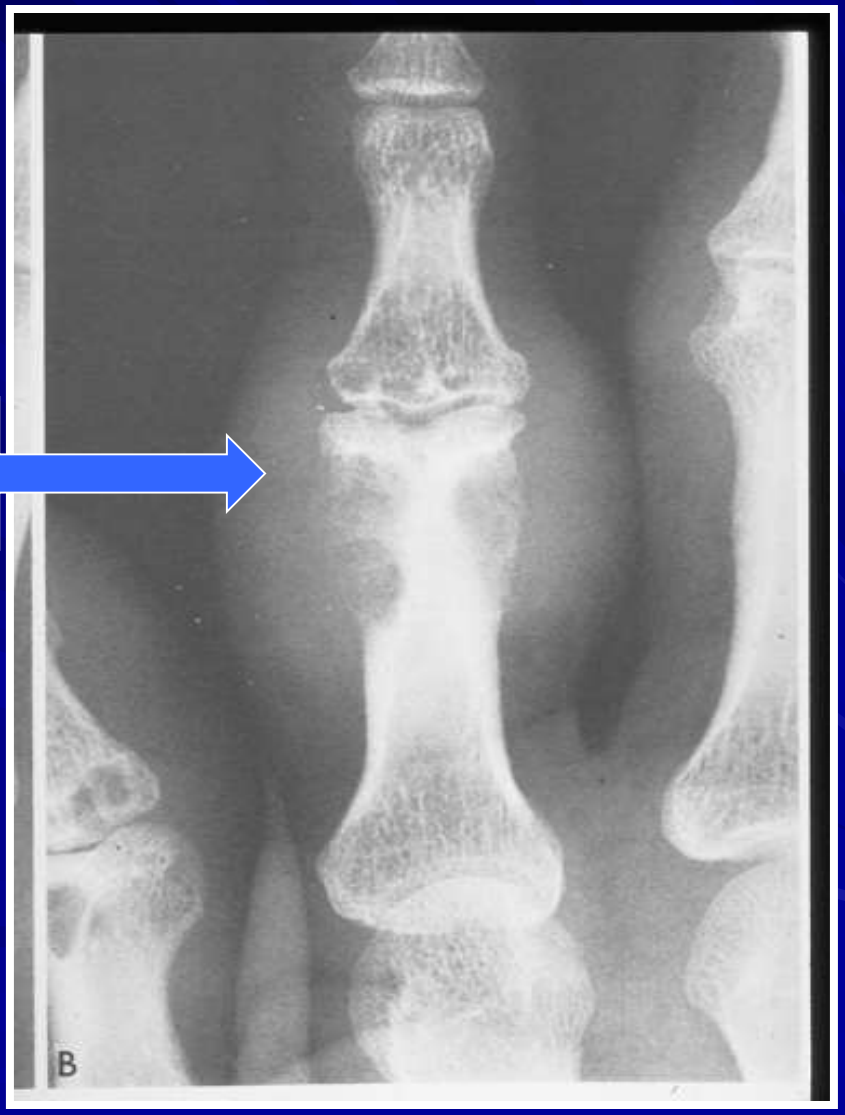
- Increasingly uncommon due to current medications
- Joints become stiff, enlarged and deformed with extensive bone and joint destruction
- Presence of tophi (large multiple urate deposits)



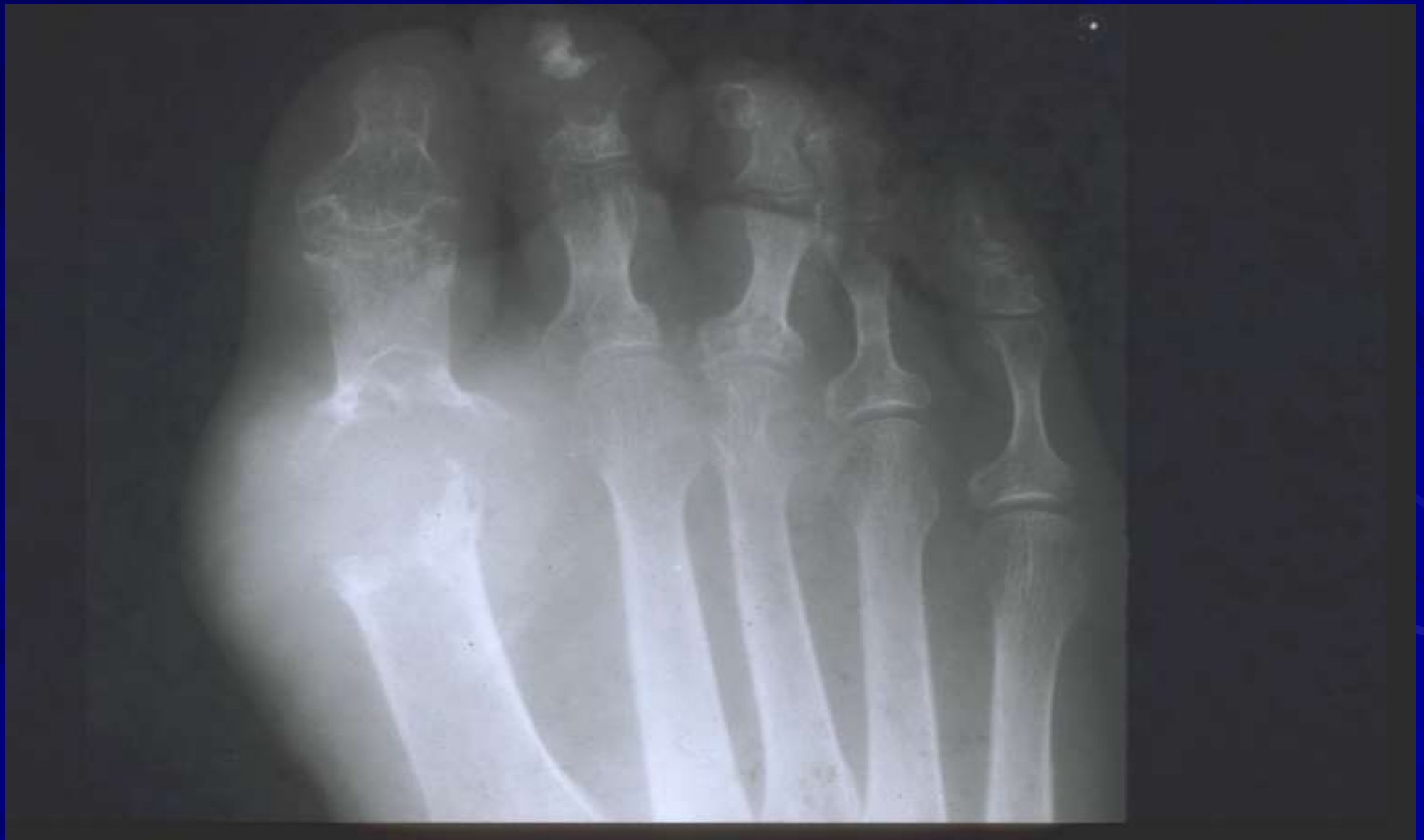
Gouty Arthritis



Note the peri-articular swelling & erosions with sparing of the joint

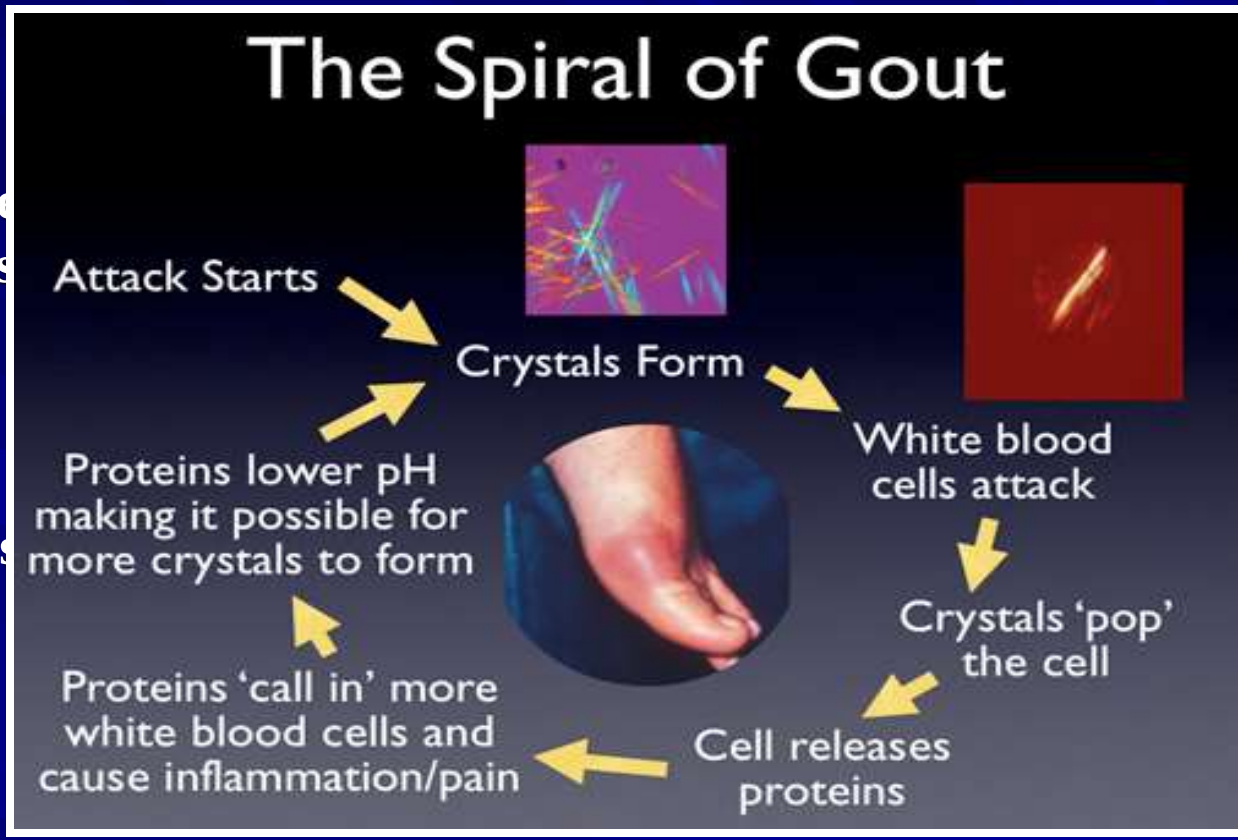


Gouty Arthritis

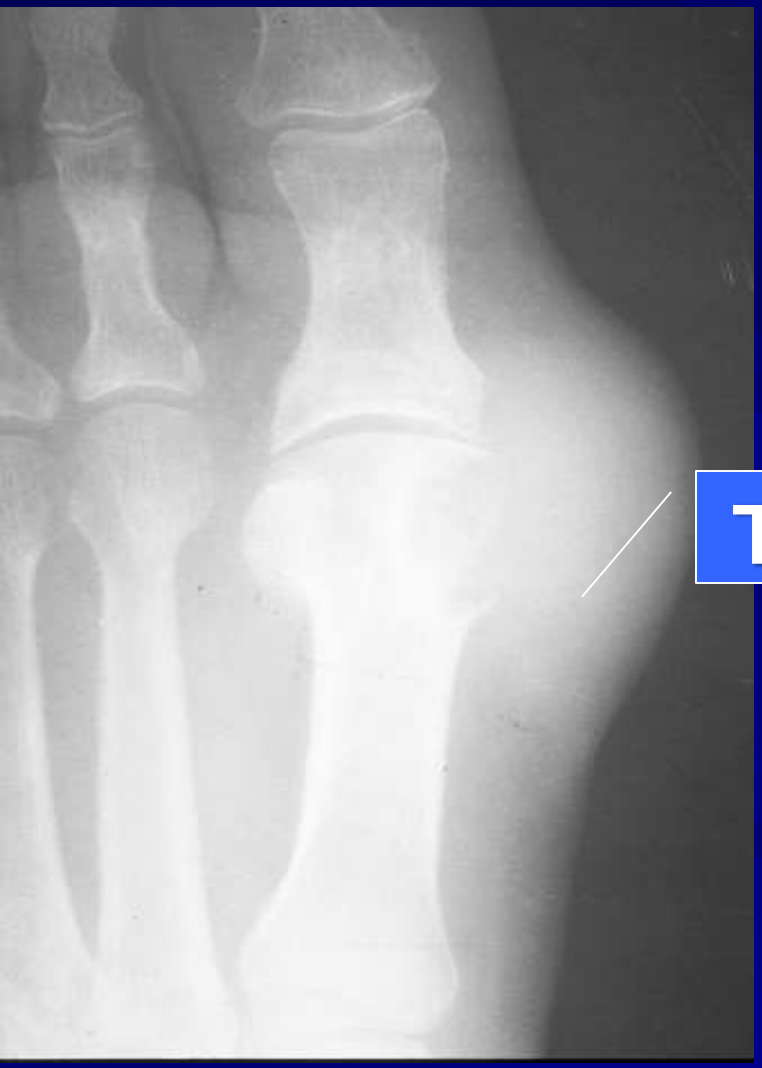


Gouty Arthritis

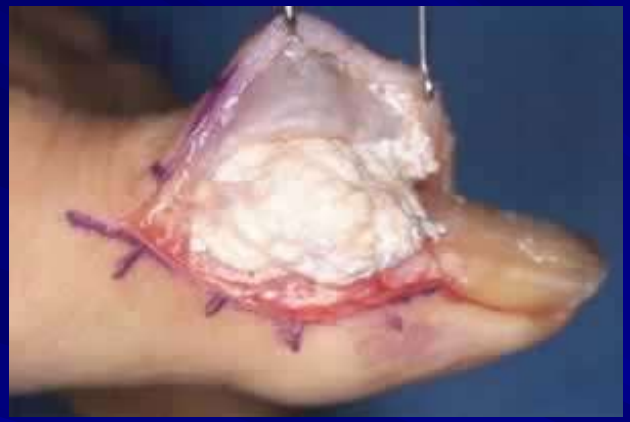
- First MPJ most often affected
  - Low pH (acidic) & low temperature can trigger urate crystal precipitation in tissues
  - Arthritic degeneration and increased vascularity
- X-ray findings appear late in disease usually after several years and multiple attacks and diagnosis already established
- Radiographs of little diagnostic value early
  - Rule out septic or infectious arthritis

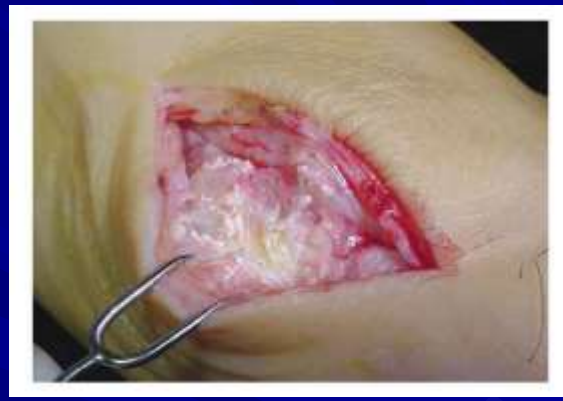


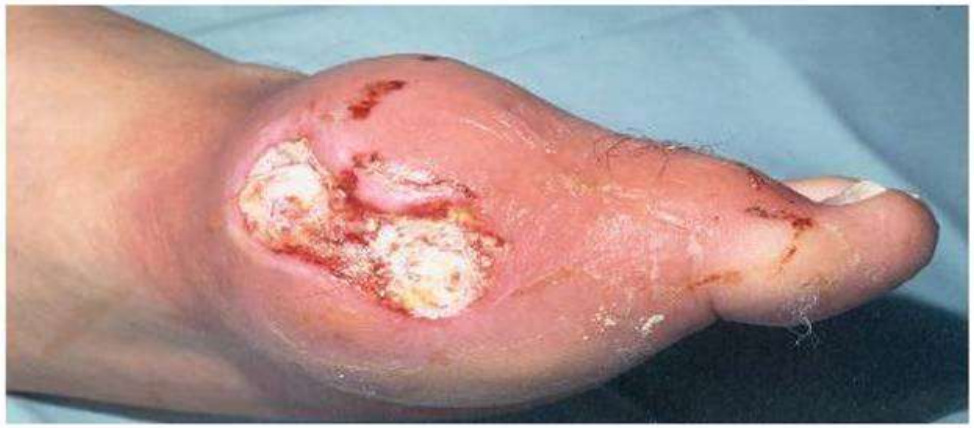
Gouty Arthritis



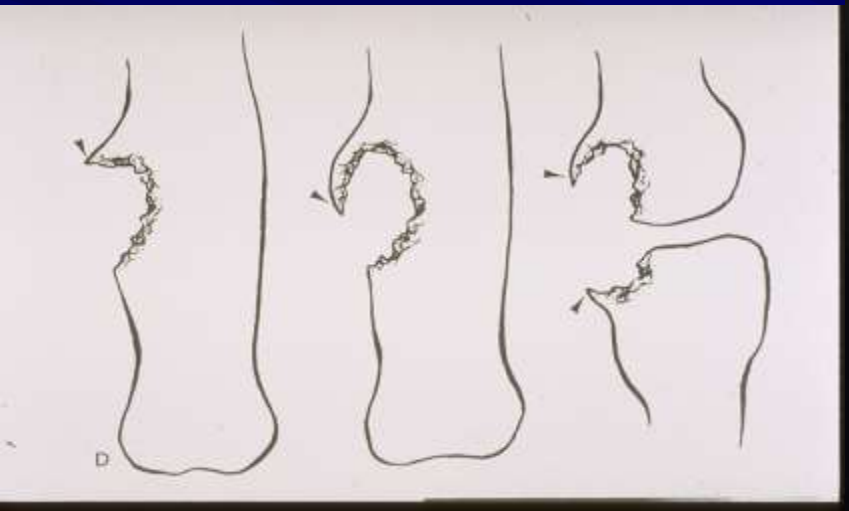
Tophi

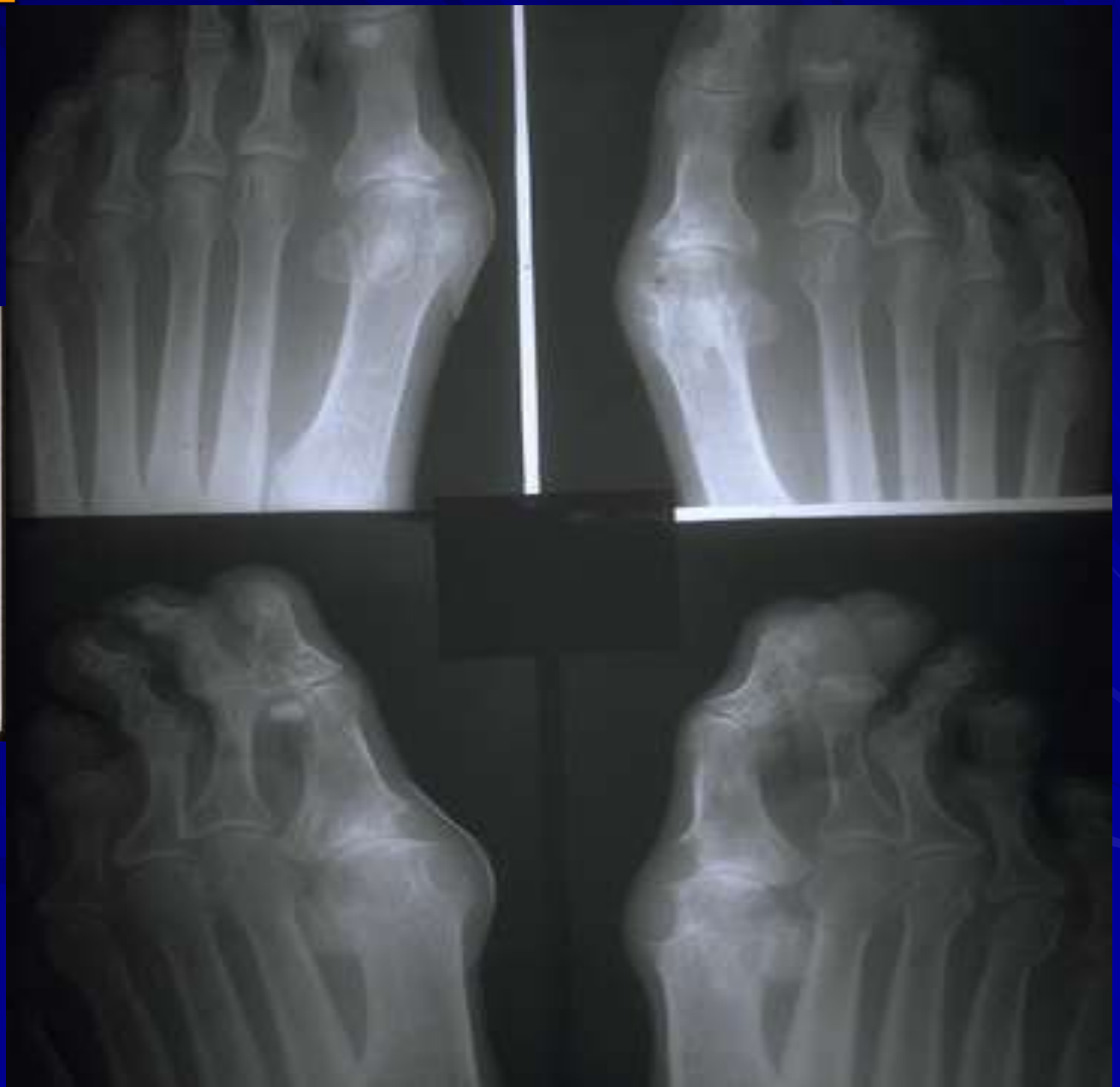






Martel's Sign





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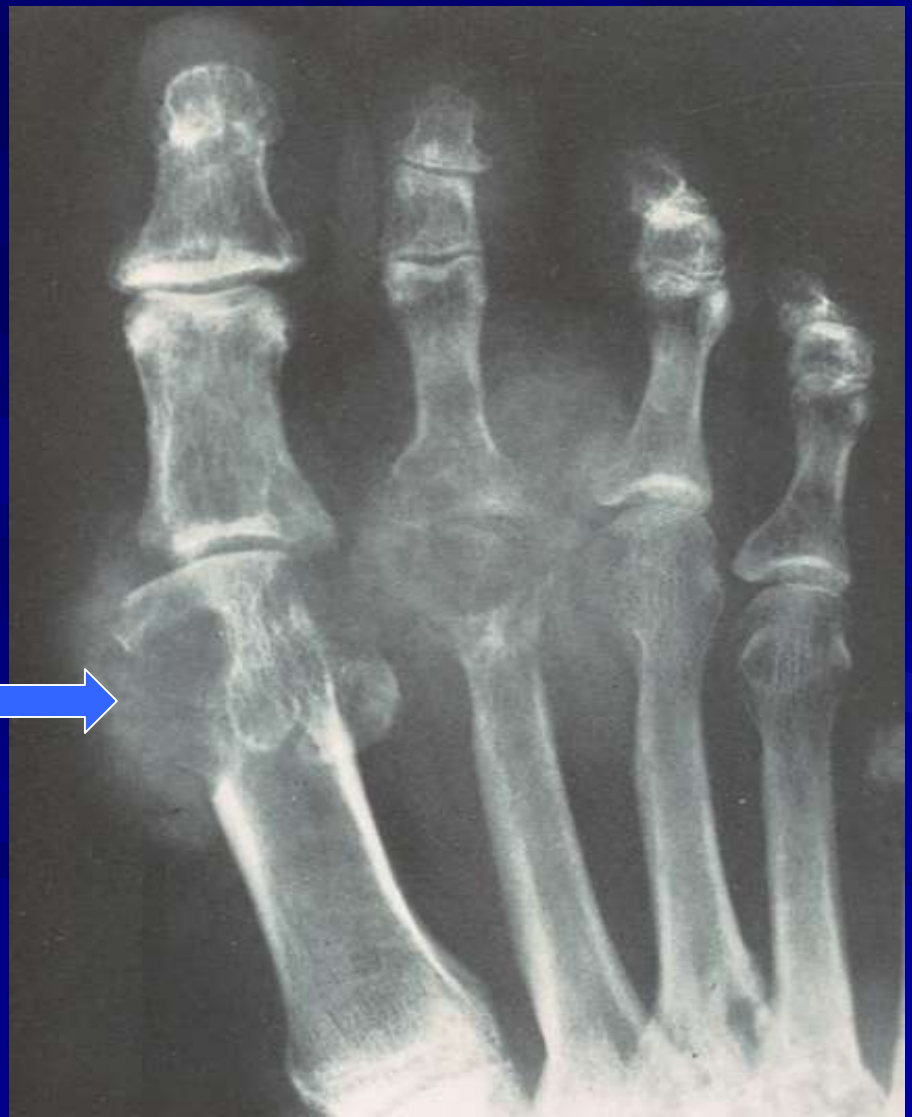
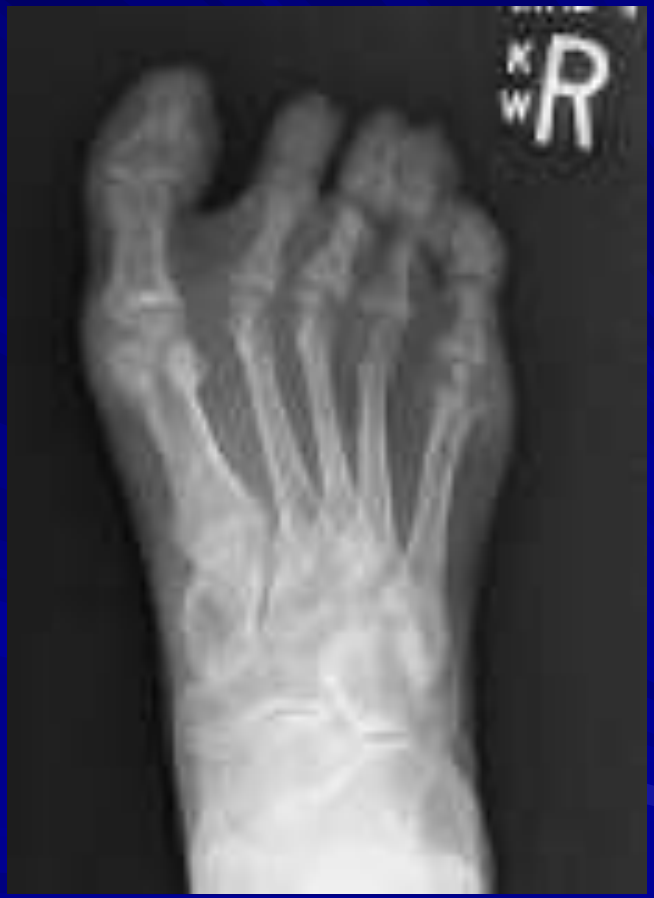
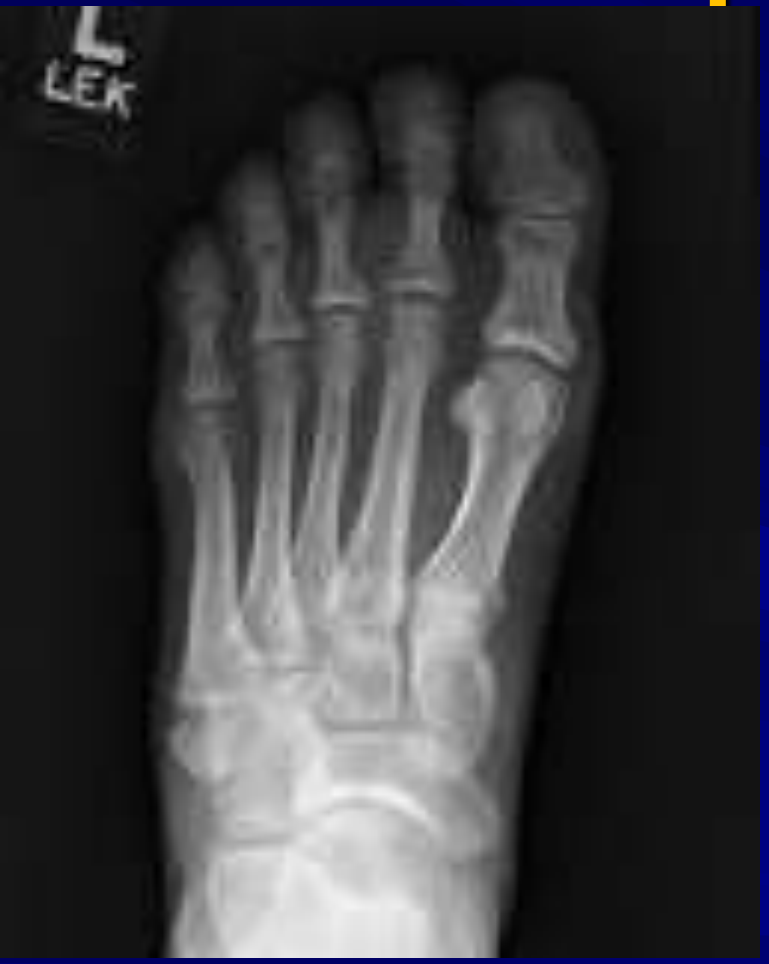


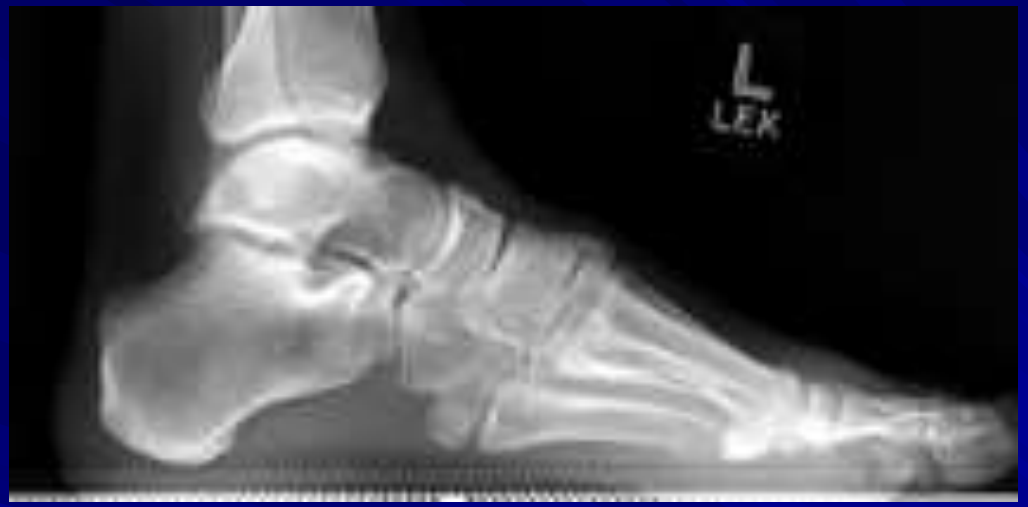
Tophi forming away from the 1st MPJ

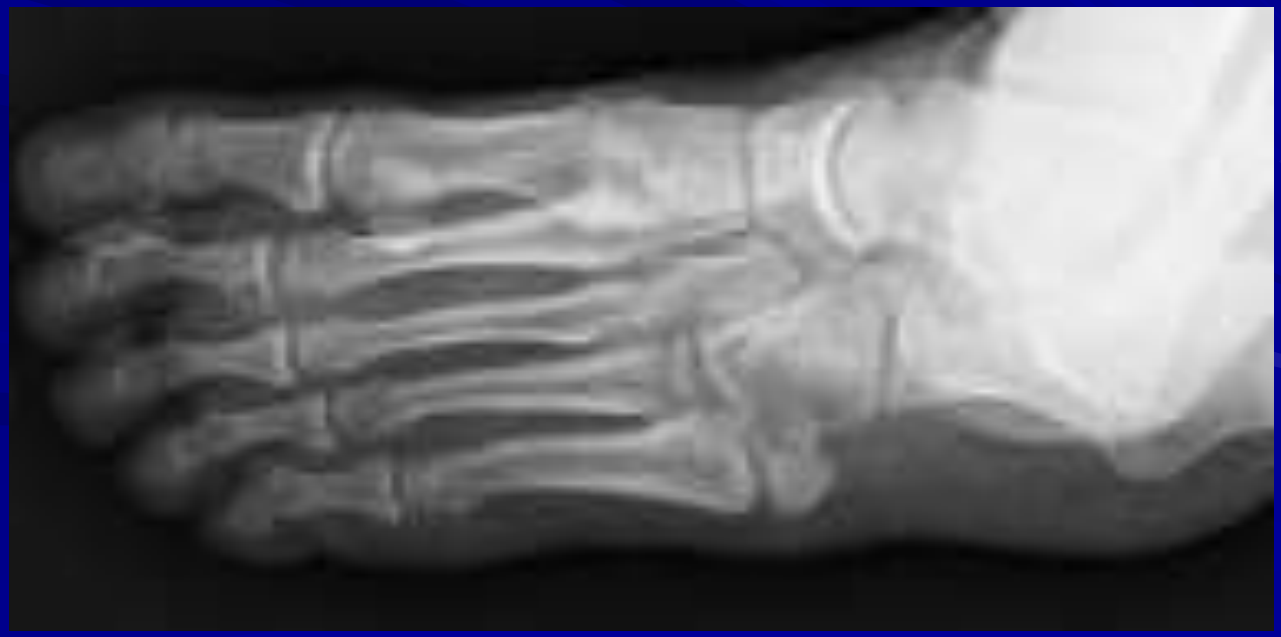
- Note extra-articular erosions of lesser metatarsal heads.



Gout Masquerading as a Neuroma

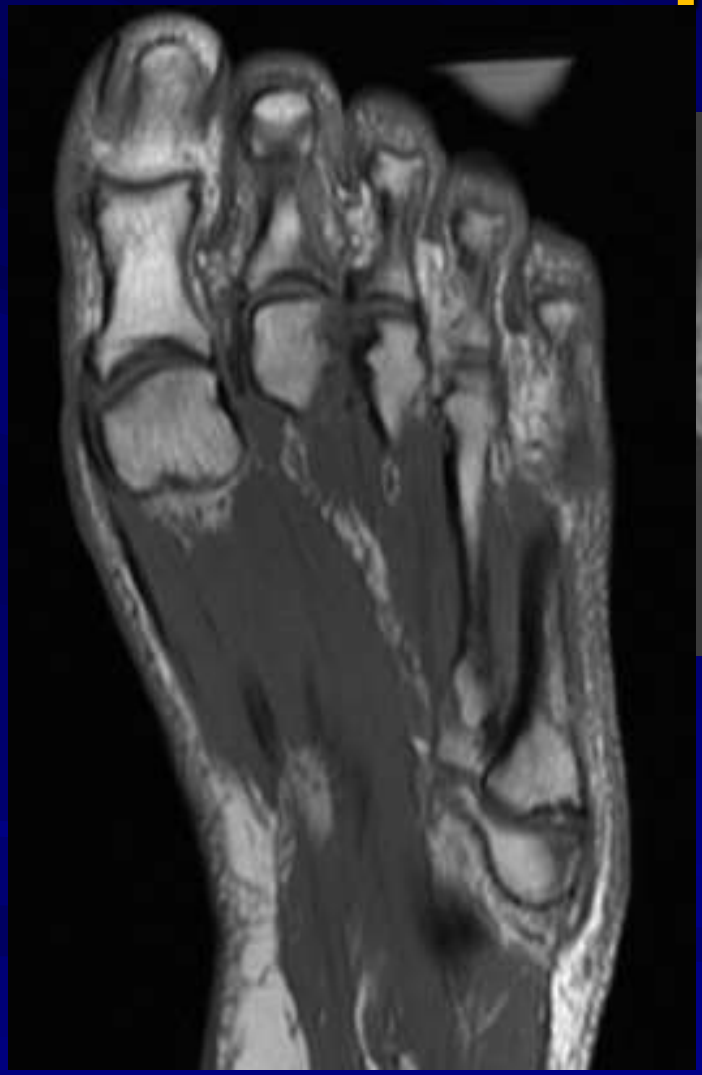


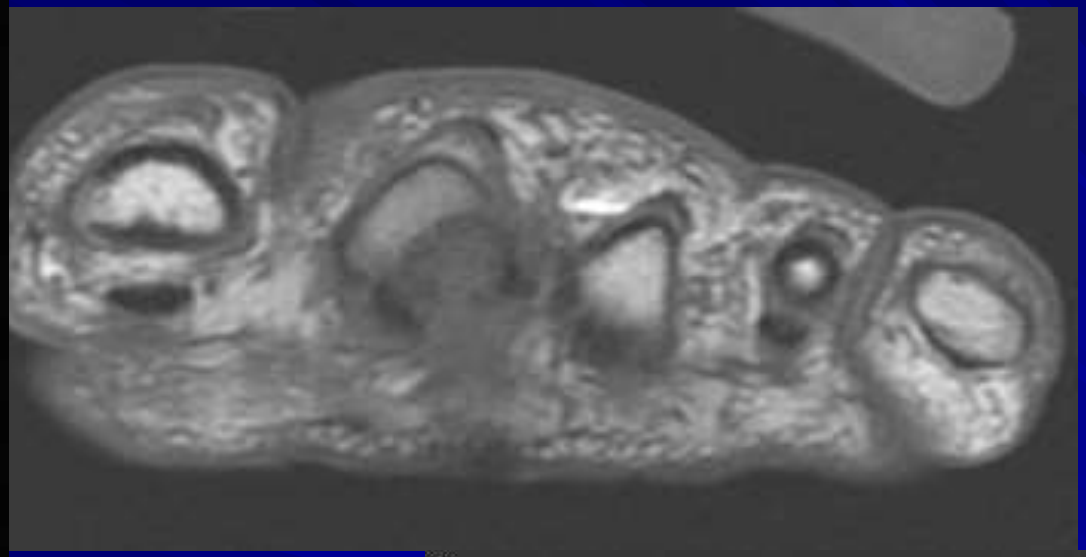


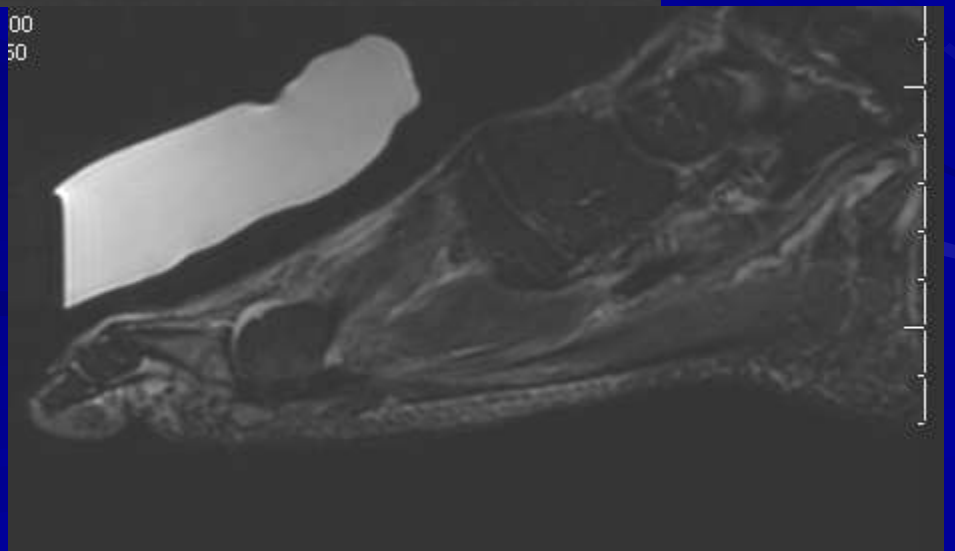


Courtesy Gina Painter, DPM Great Falls, MT

Gout Masquerading as a Neuroma

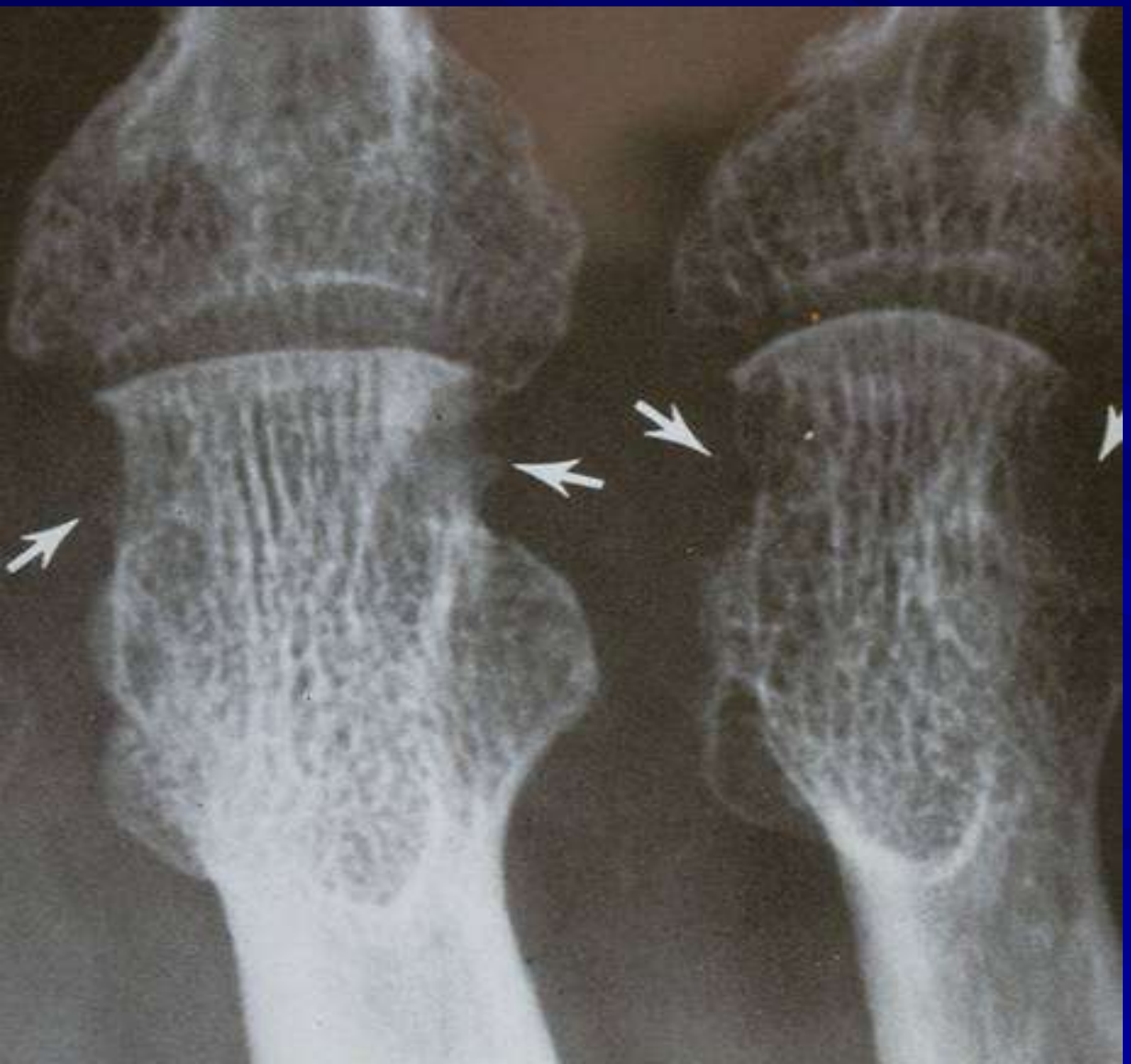




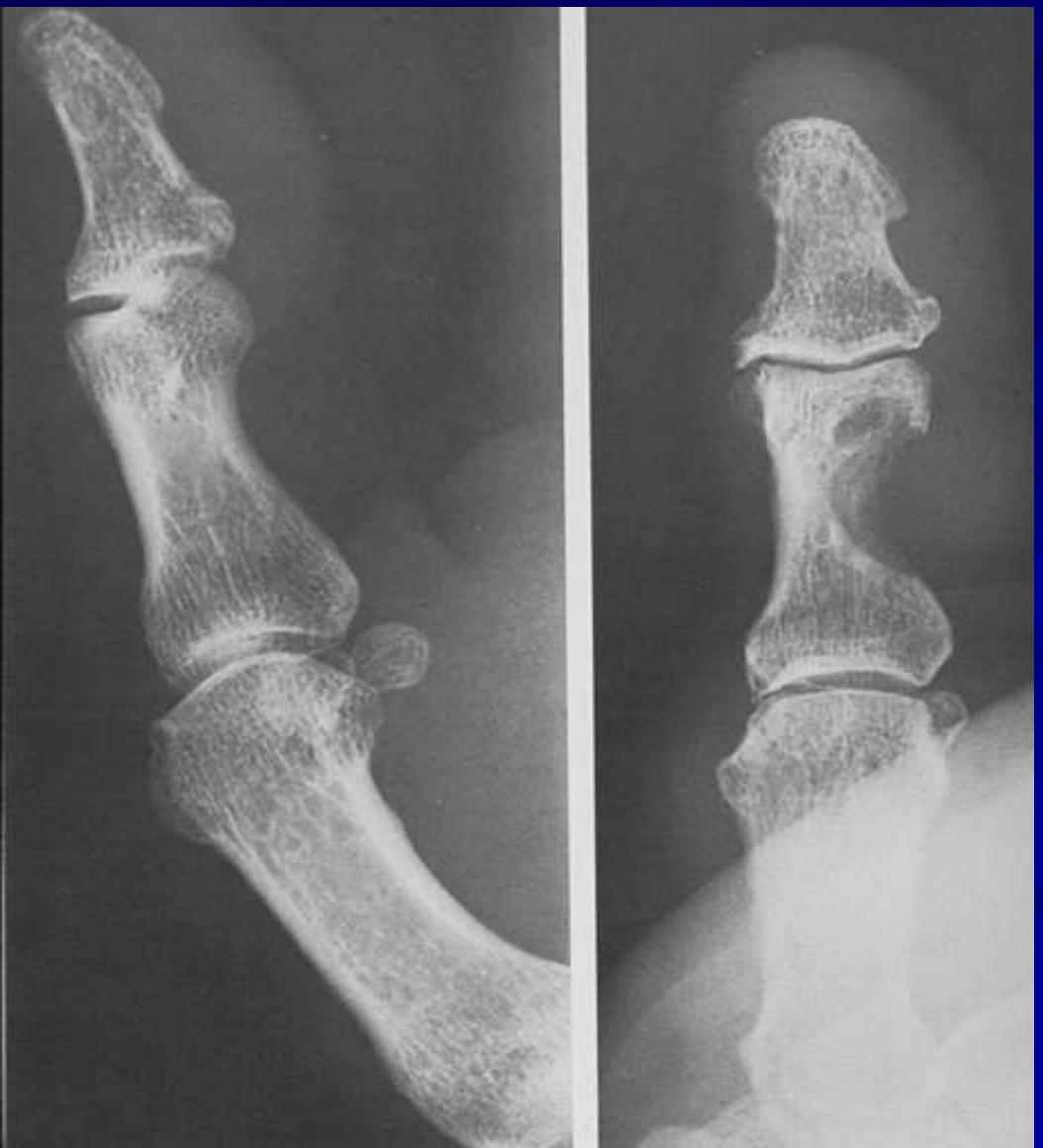


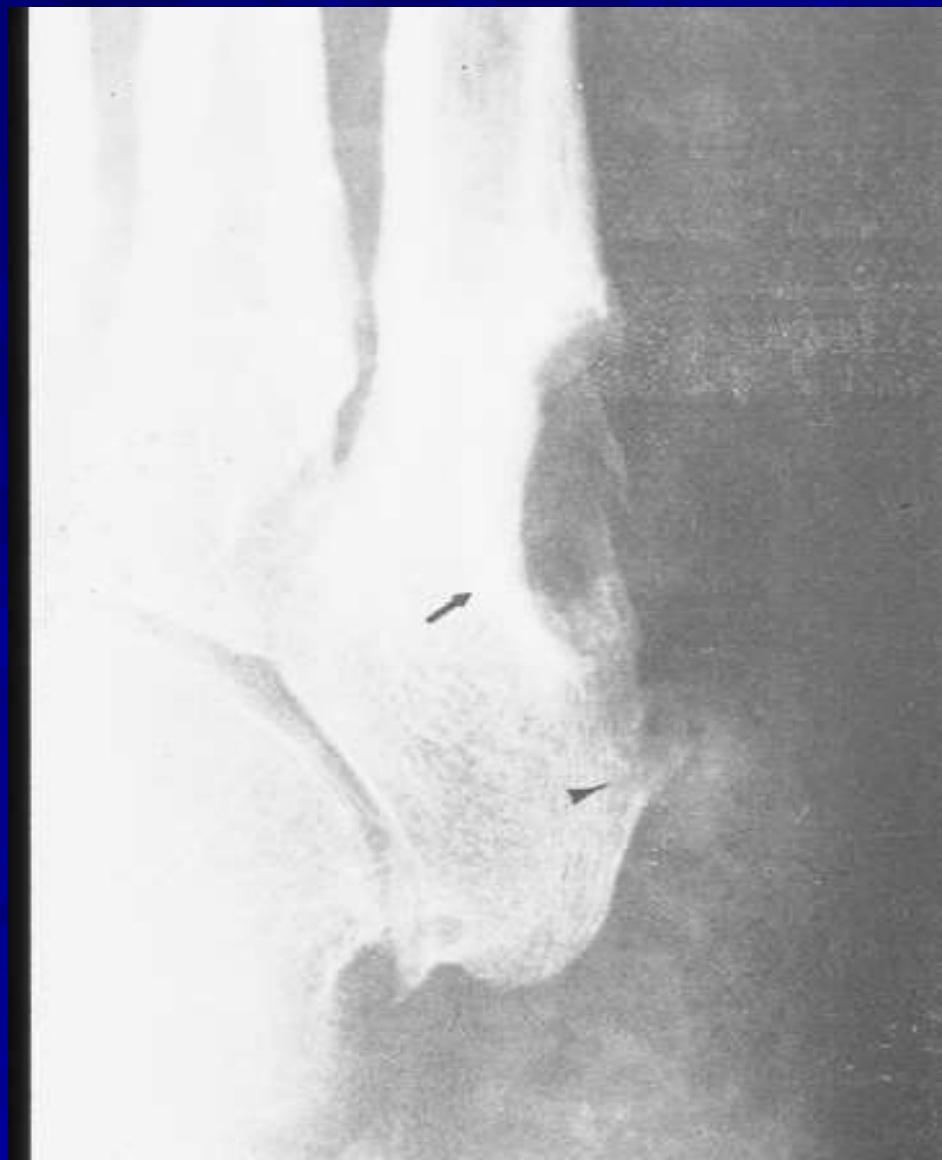
Courtesy Gina Painter, DPM Great Falls, MT

Gouty Arthritis

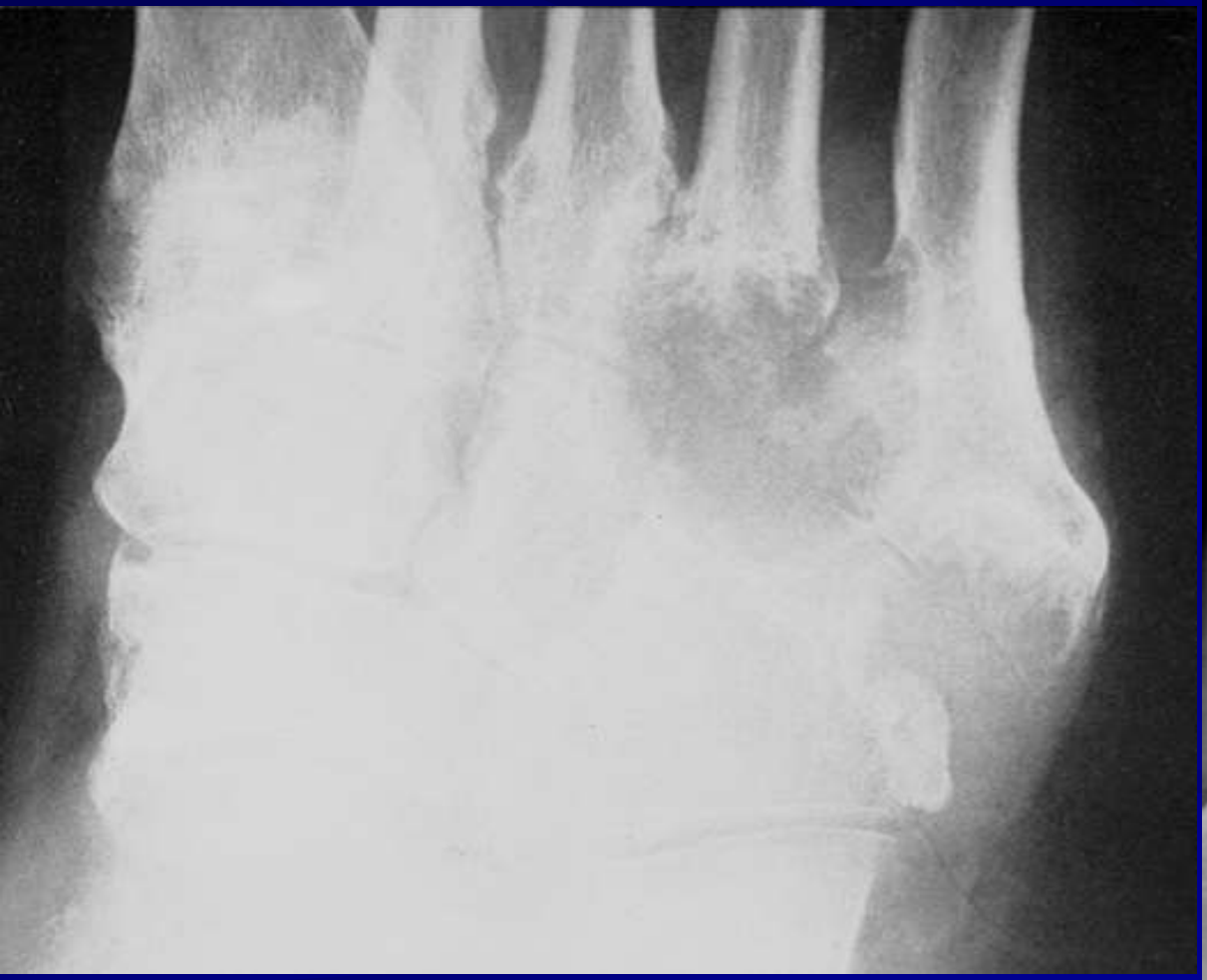


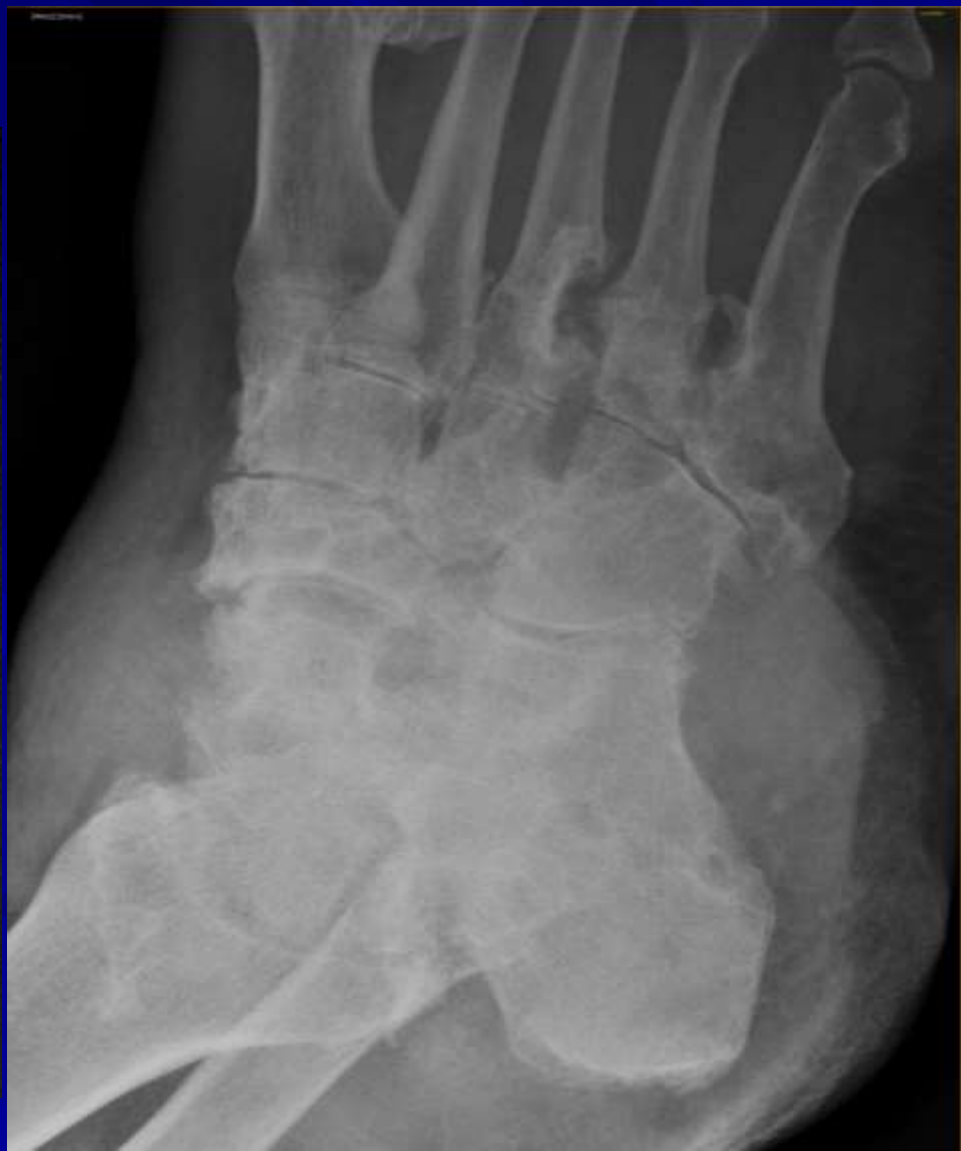
Gouty Arthritis



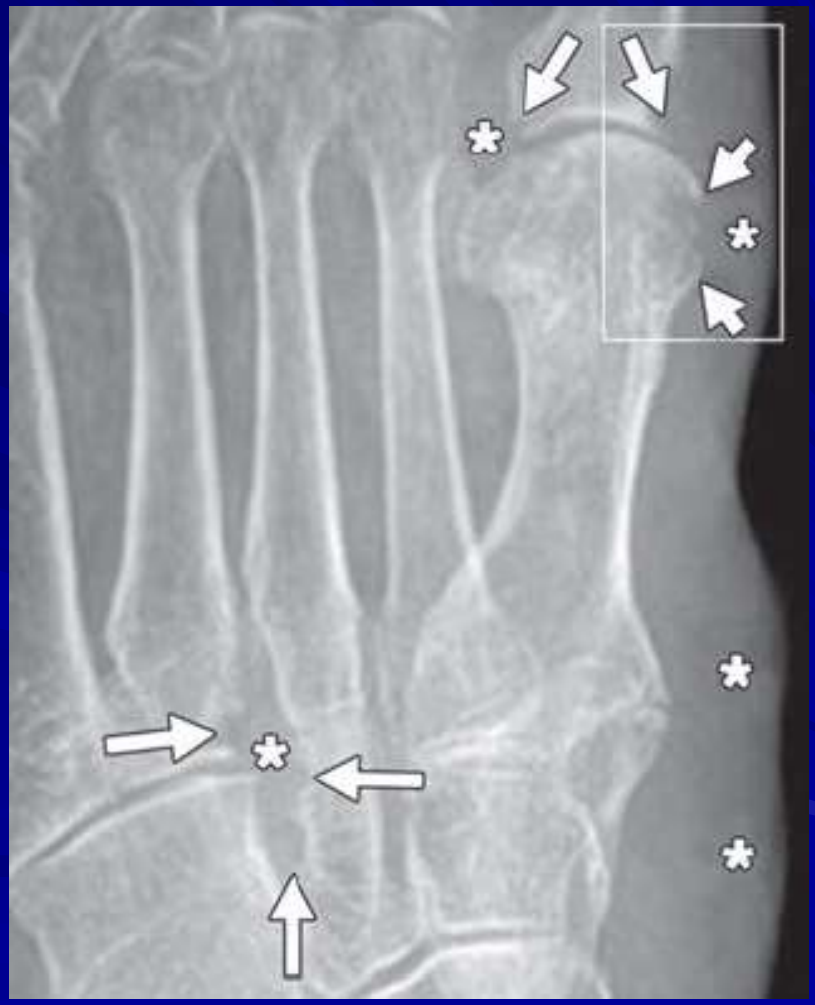


Gout – "The Great Imitator"



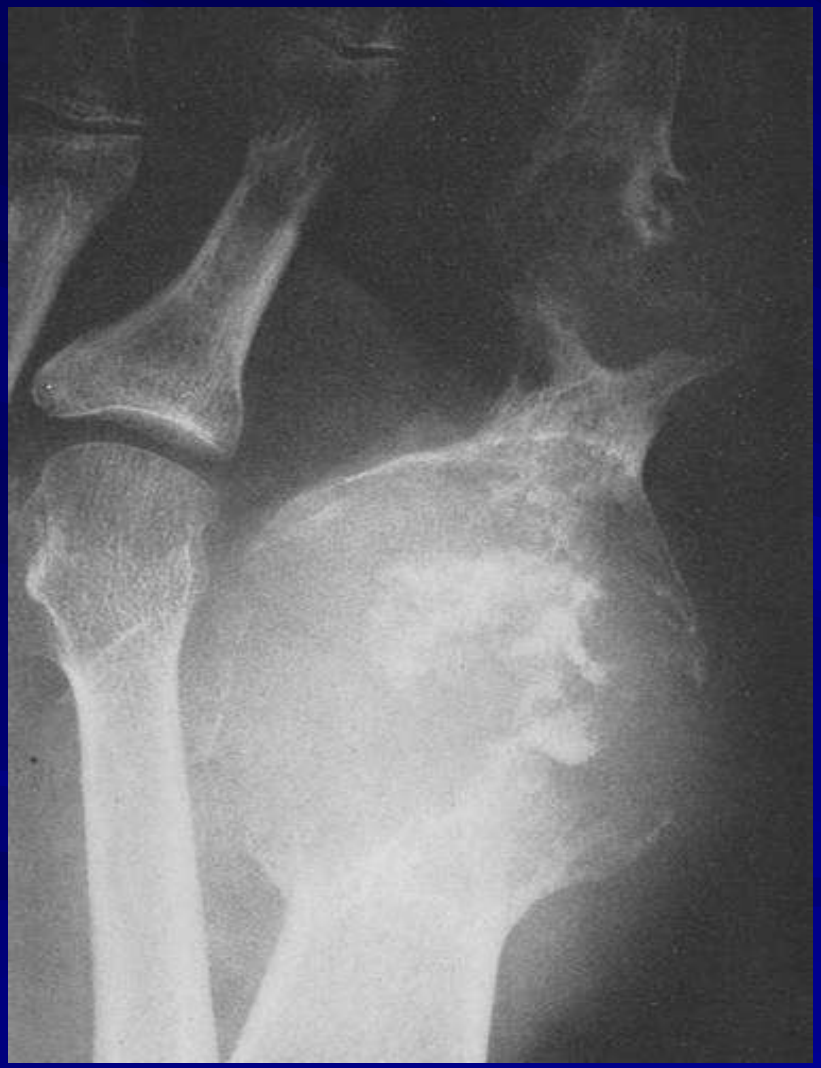


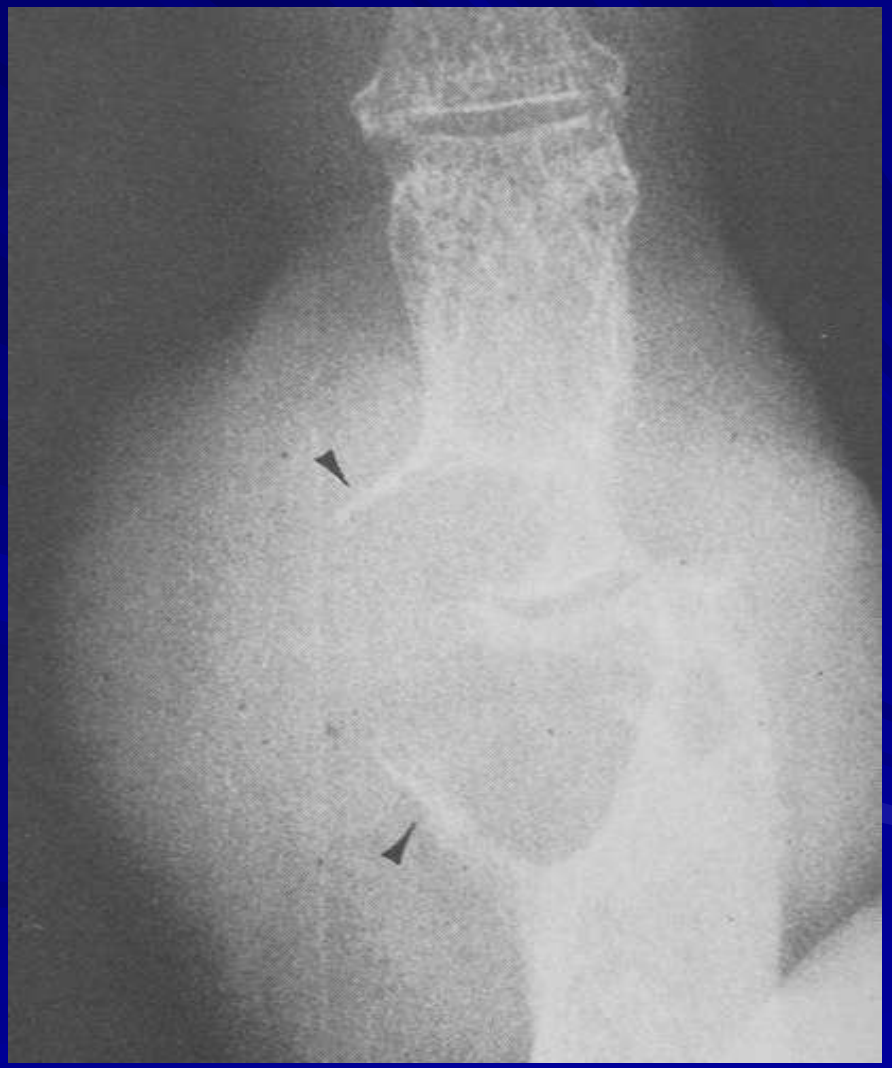
- Lis Franc Joint involvement is under-reported.



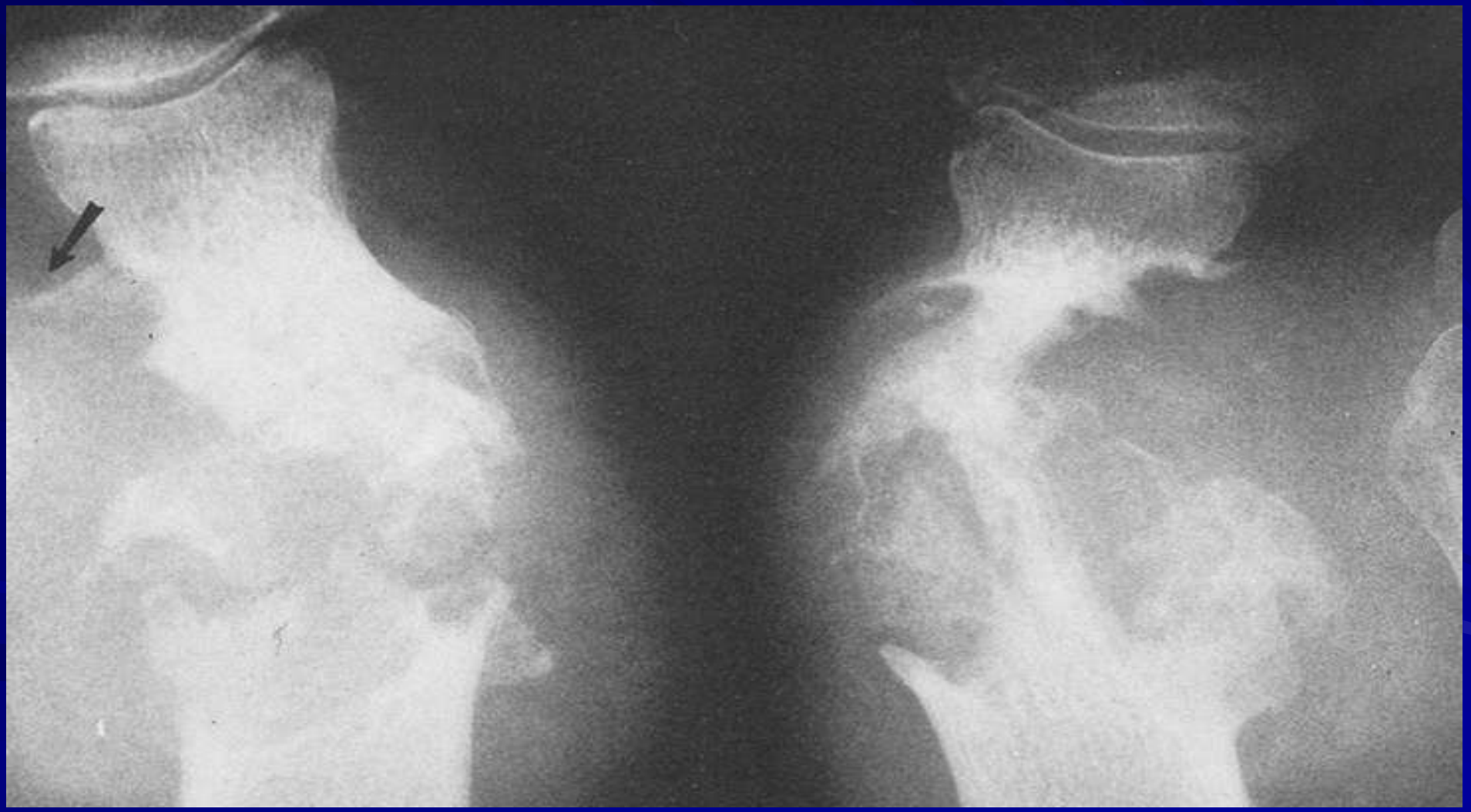
Advanced Imaging in Gout: Girish G, Glazebrook KN, Jacobson JA
AJR:201, Sept. 2013

Gout –"The Great Imitator"





Gout – "The Great Imitator"



MRI

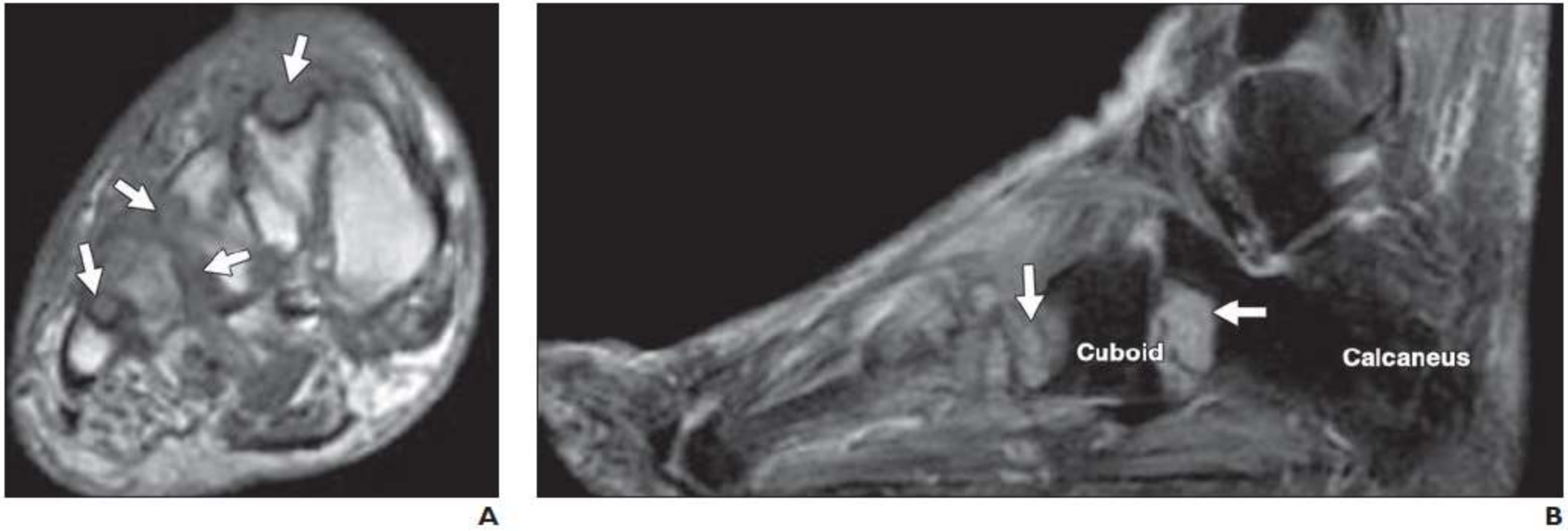


Fig. 11—56-year-old man with foot pain and gout.
A and **B**, Coronal T1-weighted (**A**) and sagittal STIR (**B**) MRI scans show multiple tophi and erosions of tarsal bones (*arrows*), which appear as intermediate signal-intensity on T1-weighted and STIR images.

DECT (Dual Energy CT) Scan

- Ct scan which utilizes both the normal X-ray as well as a second less powerful X-ray to make the images. (140 and 80 kVP).
- Assesses attenuation properties of Uric acid deposits.
- Able to differentiate monosodium urate crystals from calcification.

Advanced Imaging in Gout: Girish G, Glazebrook KN, Jacobson JA
AJR:201, Sept. 2013

DECT Scan

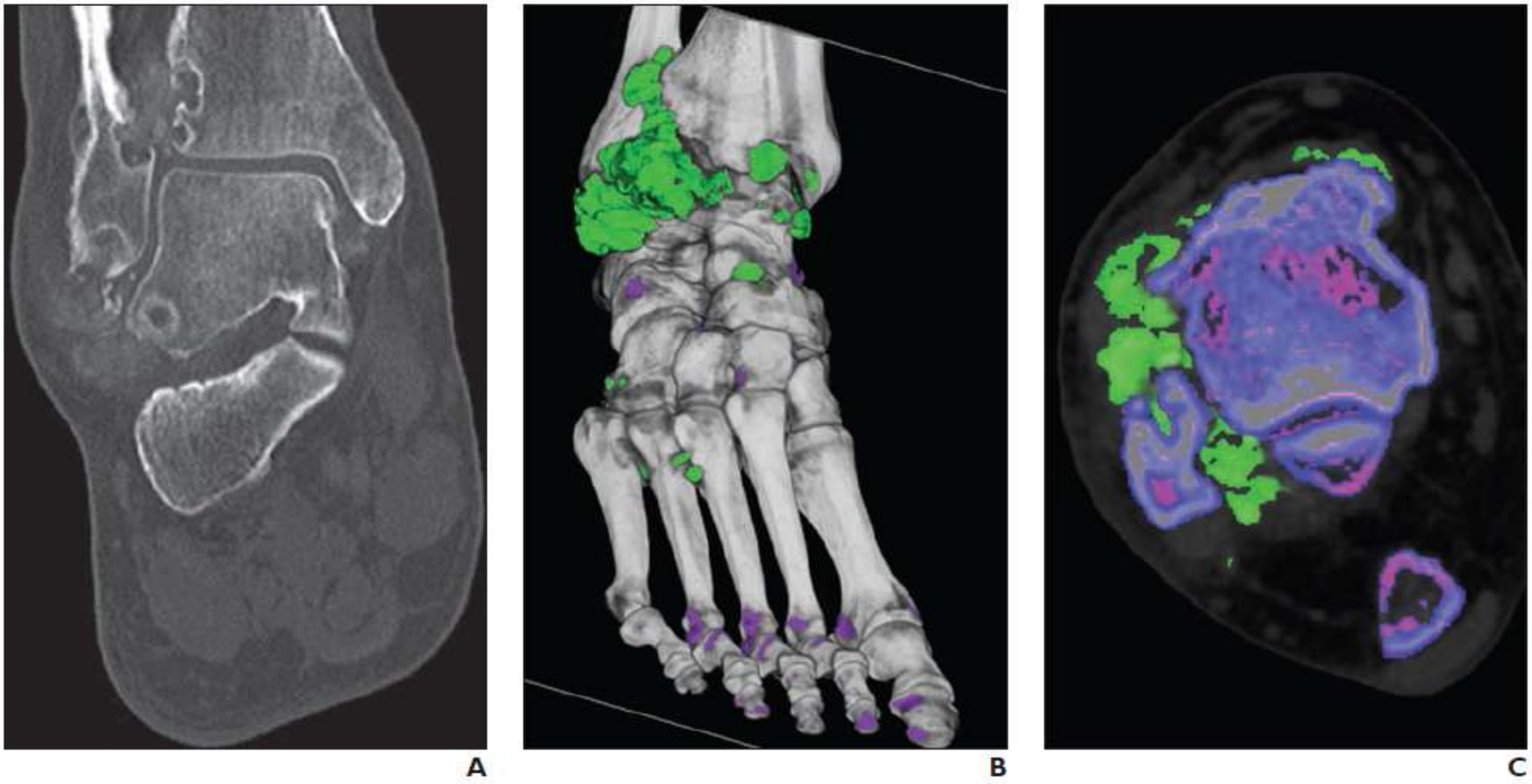
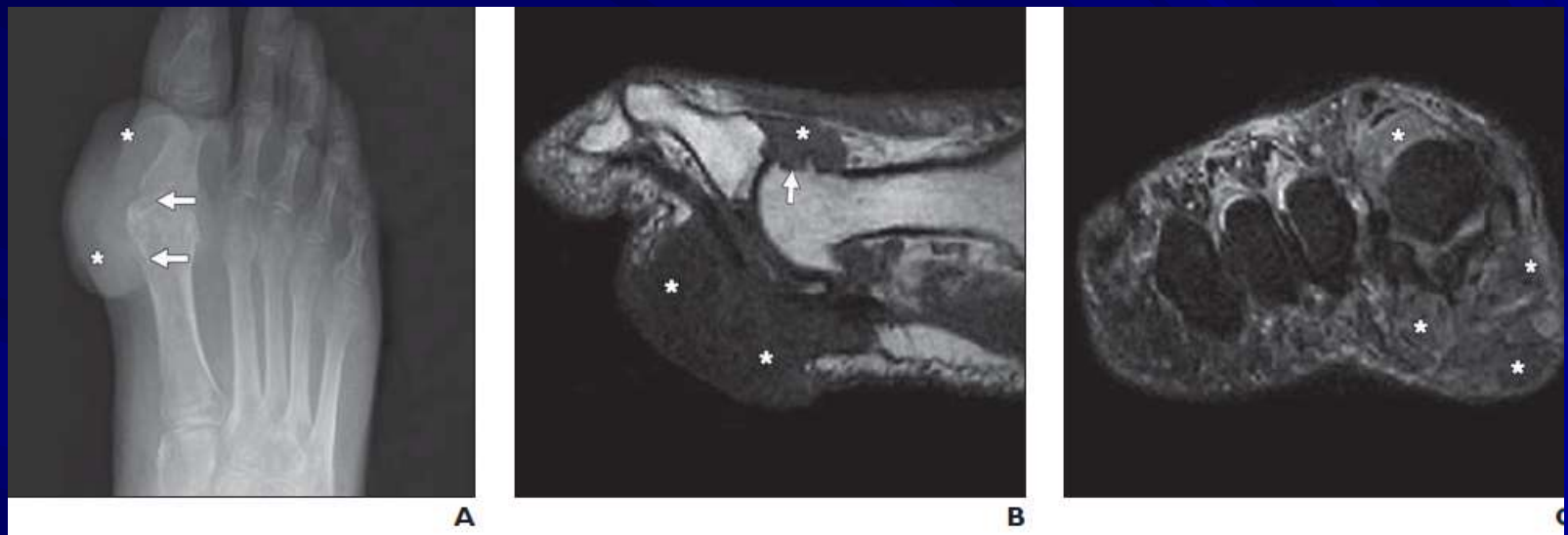
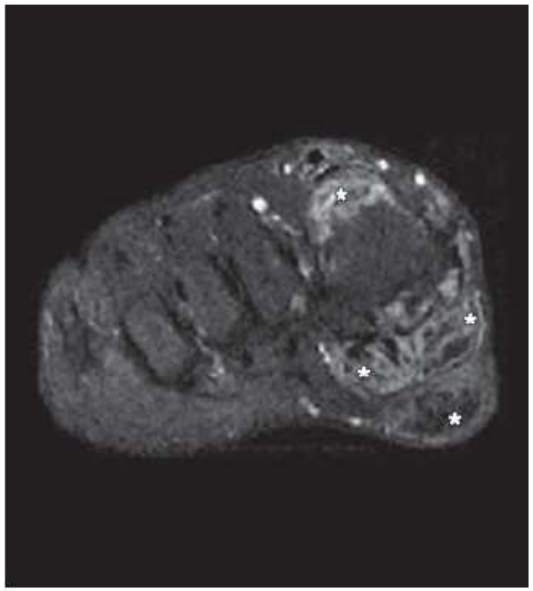


Fig. 7—42-year-old man with right ankle pain.
A, Coronal multiplanar reformmated 2D CT image of right ankle and foot shows high-attenuation tophi associated with erosions in distal tibia, fibula, and talus.
B, Axial 2D dual-energy CT (DECT) with color mapping shows uric acid deposits (*green*) in periarticular tissues of ankle, extending into erosion in anterior fibula.
C, Three-dimensional DECT with color mapping shows uric acid depositions (*green*) within ankle joint and midfoot.

Advanced Imaging in Gout: Girish G, Glazebrook KN, Jacobson JA
AJR:201, Sept. 2013

70 y/o referred for amputation of forefoot mass.





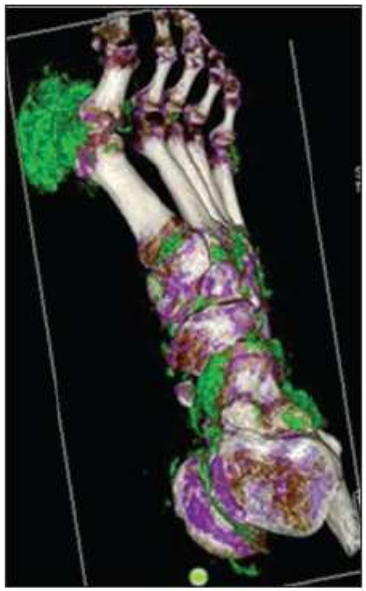
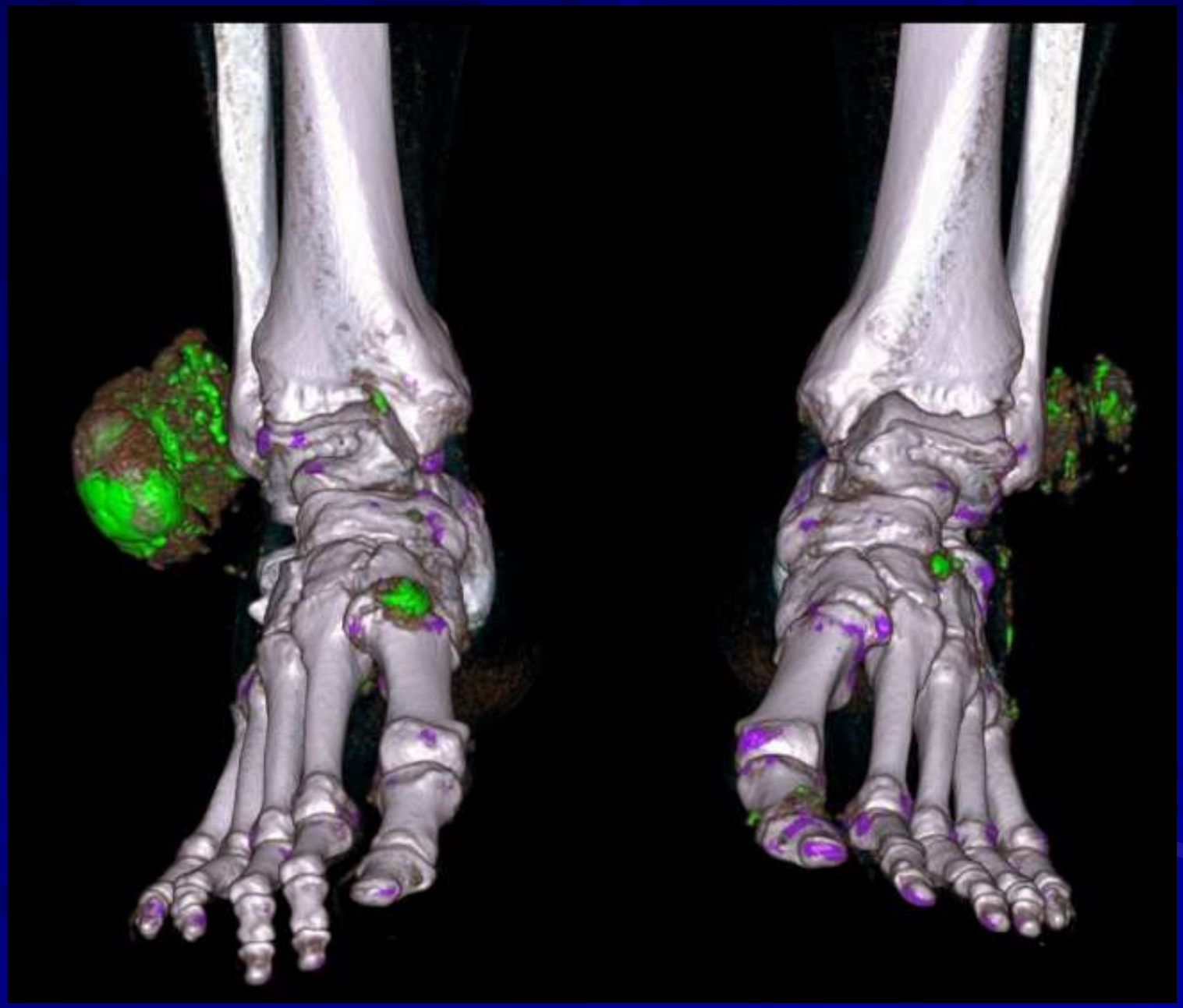


Fig. 10—70-year-old man referred for amputation of forefoot for mass.
A, Radiograph of right foot shows soft-tissue mass (*asterisks*) adjacent to right first metatarsophalangeal joint (*arrows*).
B, Sagittal T1-weighted MRI of right forefoot shows intermediate-signal-intensity soft-tissue mass (*asterisks*) surrounding first metatarsophalangeal joint, with adjacent erosion in first metatarsal head (*arrow*).
C and **D,** Coronal inversion recovery (**C**) and contrast-enhanced spoiled gradient T1-weighted fat-saturated MRI (**D**) of forefoot through level of metatarsal heads show enhancing and heterogeneous soft-tissue masses (*asterisks*).
E, Three-dimensional rendered dual-energy CT with color mapping shows extensive monosodium urate (MSU) crystal deposition (*green*) consistent with tophaceous gout about first metatarsophalangeal joint, with additional unsuspected MSU deposition in ankle and midfoot.

DECT: Dual Energy CT

- 3D rendered DECT with color mapping demonstrates MSU Crystals (green) consistent with tophaceous gout.



Dual-energy CT in Gout – A review of current concepts and applications.
H Chou, T Chin, W Peh. J Med Radiat Sci: 2017 Mar, 64(1): 41-51

TREATMENT

7 Best Essential
Gout Treat

Birch Esse

Wintergr

Capsaic

Peppern

Gout is a form of arthritis, mostly that has known cause, namely the buildup of crystalline uric acid deposits in the joints and the blood.

Natural Remedies For Gout

The Farmacy

	Apple Cider Vinegar Mix 1–2 tbsp in 8 oz Water		Drink Beet Juice
	Baking Soda Mix 1/2 tsp in 8oz Water *Do Not Use If You Suffer From Hypertension		Have Some Bromelain
	Consume Cherries		Reduce Alcohol Consumption
	Eliminate Sugar And Soda		Up Your Vitamin C Intake
	Hydrate		Reduce Caffeine Intake

ut Relief
est Natural Remedies

ELERY SEEDS
elps lower
ric acid

QUERCETIN
helps lower uric acid

MULBERRY
hibits urate in
idneys

BROMELAIN
relieves swelling, inflammation

RUTIN
nti-
flammatory

BURDOCK
helps eliminate uric acid

NETTLE
nti-
flammatory

TURMERIC
natural pain relief

DEVIL'S CLAW
ain relief

CAPSAICIN
natural topical pain relief

More at Goutezol.com

TREATMENT

- Rest
- Ice
- Elevation
- Avoid constrictive sheets/hose/shoe gear
- Gait assistive devices

Ice Therapy During Gout Attack

OBJECTIVE:
To evaluate the effect of local application of ice on duration and severity of acute gouty arthritis.
METHODS:
Nineteen patients with acute gout were enrolled and randomized into 2 groups. Group A (n = 10) received topical ice therapy, oral prednisone 30 mg PO tapered to 0 over 6 days and colchicine 0.6 mg/day. Group B was the control group (n = 9), given the same regimen but without the ice therapy. The patients were followed for one week.
RESULTS:
The mean reduction in pain for those patients treated with ice therapy was 7.75 cm (on 10 cm visual analog scale) with standard deviation +/- 2.58 compared with 4.42 cm (+/- SD 2.96) for the control group. Using a Wilcoxon rank-sum test there was a significant difference (p = 0.021) in pain reduction between the ice therapy and control groups.
CONCLUSION:
The group treated with ice had a significantly greater reduction in pain compared with the control group. Although the clinical improvement was impressive, due to the small sample size we could not show statistically significant improvement in all the variables that tended to suggest that effect was more than simply analgesic. Cold applications may be a useful adjunct to treatment of acute gouty arthritis.

Local ice therapy during bouts of gouty arthritis:
Schlesinger N, Detry MA, Holland BK, et.al.
J Rheumatol. 2002 Feb;29(2):33-14

Coffee and Gout

- Males >40.
  - Studied over a period of 12 years.
  - N = 45,869
- Drinking 1-3 cups/day lowered gout risk by 8%.
- Drinking 4-5 cups/day lowered gout risk by 40%.
- Drinking > 5 cups lowered gout risk by 59%.
- Drinking Decaf coffee lowered the effect.
- Drinking Tea did not appear to have a protective affect.

Choi, Hk, Curhan G. Coffee, tea and caffeine consumption and serum uric acid: the Third National Health and Nutrition Examination Survey. Arthritis Rheum. June 2007

TREATMENT

- Indocin
- Colchicine
- NSAID’s
- Corticosteroids
- Allopurinol

INFORMAL POLL

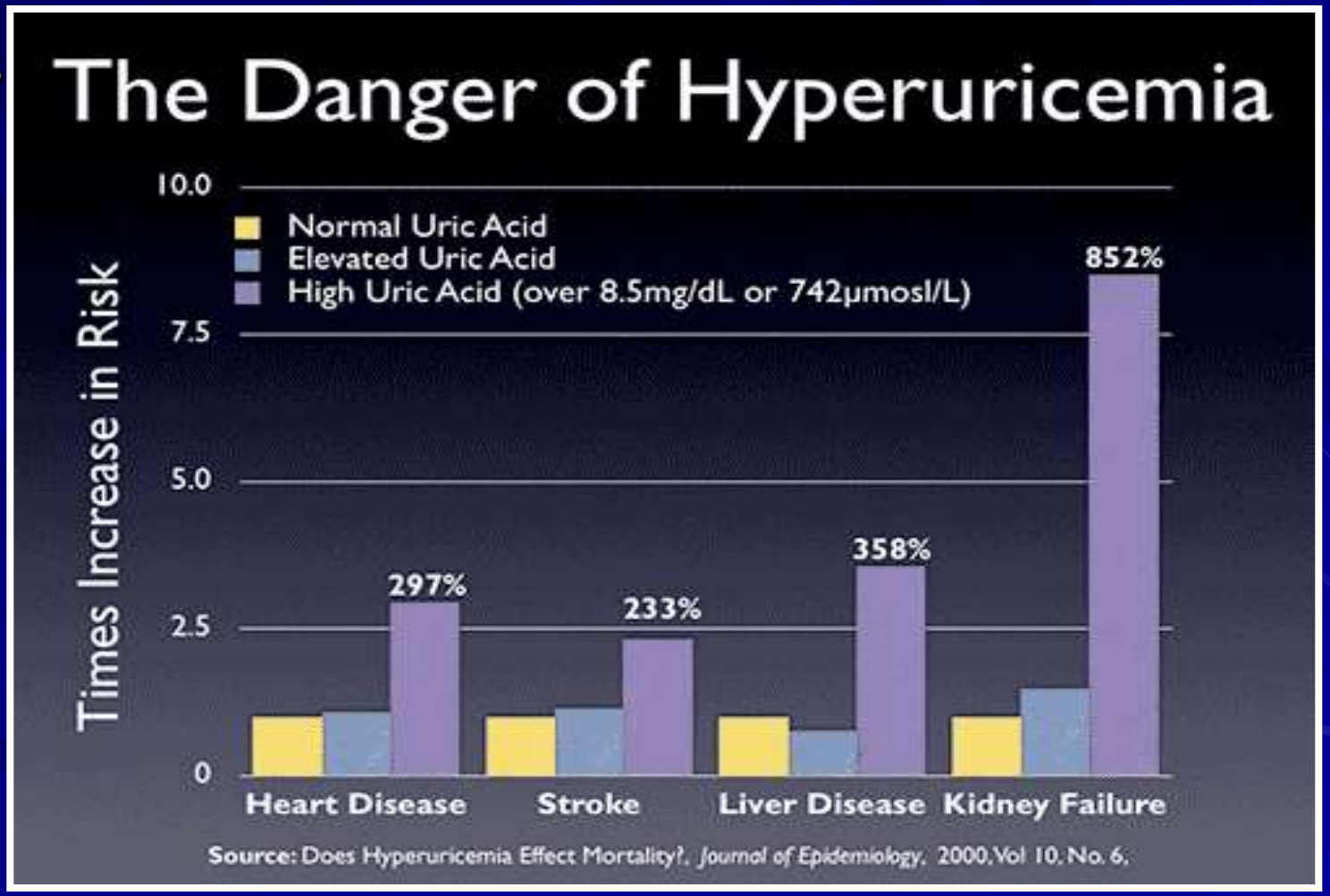
Podiatry Management Survey June 2018

- Do you prescribe Uric Acid lowering drugs for the management of acute or chronic gout?
  - Yes, for acute gout. 27.91%
  - Yes, for chronic gout. 6.18%
  - Yes, for acute and chronic gout. 25.64%
  - No 40.27%

  - N=971

Systemic Risk

- Increased levels of Uric Acid and associated Systemic Disease.



Evidence Based Medicine and the Treatment of Gout

DANIEL P. EVANS, DPM, FACFAOM
Professor, Department of Podiatric Medicine and Radiology
Dr. Wm. Scholl College of Podiatric Medicine

GORDON K. LAM, MD, FACR
NorthEast Rheumatology
Medical Director, Northern Region Research Center
Atrium Health, Concord, NC

CONFLICT OF INTEREST

- Horizon Pharm, Plc: Speakers Bureau; Advisory Board
- Selecta Biosciences: Advisory Board

OUTLINE

- Gout from a Rheumatologist's Perspective
  - Treatment of Patient with Acute Gout Flare
    - Colchicine
    - Corticosteroids
    - Indocin/NSAID's
  - Long-term Management of Gout
  - Management of the Recalcitrant Patient
    - Newer Medication Options: Combination therapies, pegloticase
  - Peri-operative Management of the Gout Patient

Collaboration between podiatrists & rheumatologists

- Podiatrists' role in gout management today is critical
  - Increased emphasis on comprehensive, collaborative and correlated care amongst healthcare providers
  - "First responders" of gout flares
  - Surgical management of refractory tophaceous gout
  - Missing link between a patient's PCP & rheumatologist

Collaboration between podiatrists & rheumatologists

Lansdowne *et al. Journal of Foot and Ankle Research* (2015) 8:14
DOI 10.1186/s13047-015-0071-z

JOURNAL OF FOOT AND ANKLE RESEARCH

RESEARCH Open Access

Perceived barriers to the management of foot health in patients with rheumatic conditions

Nina Lansdowne, Angela Brenton-Rule, Matthew Carroll and Keith Rome*

Results

- Web-based survey demonstrated poor integration of podiatrists into multidisciplinary teams
- Only 16% reported being part of an established multidisciplinary team
- 95% expressed interest in professional development for the podiatric management of arthritides

Conclusions

- There are barriers in the involvement of podiatrists in the management rheumatic conditions

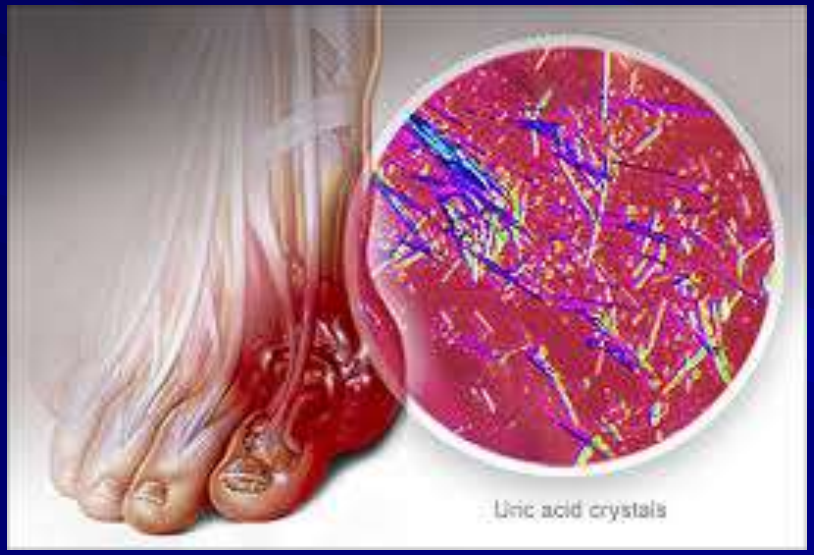
Overcoming barriers between podiatrists and rheumatologists in caring for gout patients

- Identify a local rheumatologist who has a common interest in gout
- Foster a collaborative relationship
  - Establish a procedure for direct contact to refer patients in a timely manner
  - Perform joint community outreach and education
  - Create dual podiatry-rheumatology clinics
  - Develop a co-management strategy
    - Delineate roles
    - Identify common ground

When to refer to a rheumatologist

- To confirm the diagnosis, particularly in patients with atypical presentations
- To treat chronic, uncontrolled gout
  - Inability to achieve sUA < 6.0 mgL with conventional urate-lowering therapies at appropriate doses
  - Recurrent flares despite adequate treatment
  - Comorbidities that may limit therapy (e.g. chronic kidney disease, liver disease, heart disease)
  - Complex cases refractory to conventional therapies
    - Initiation of biologic therapy

Treatment of gout



Overcoming barriers between patients and providers in caring for gout

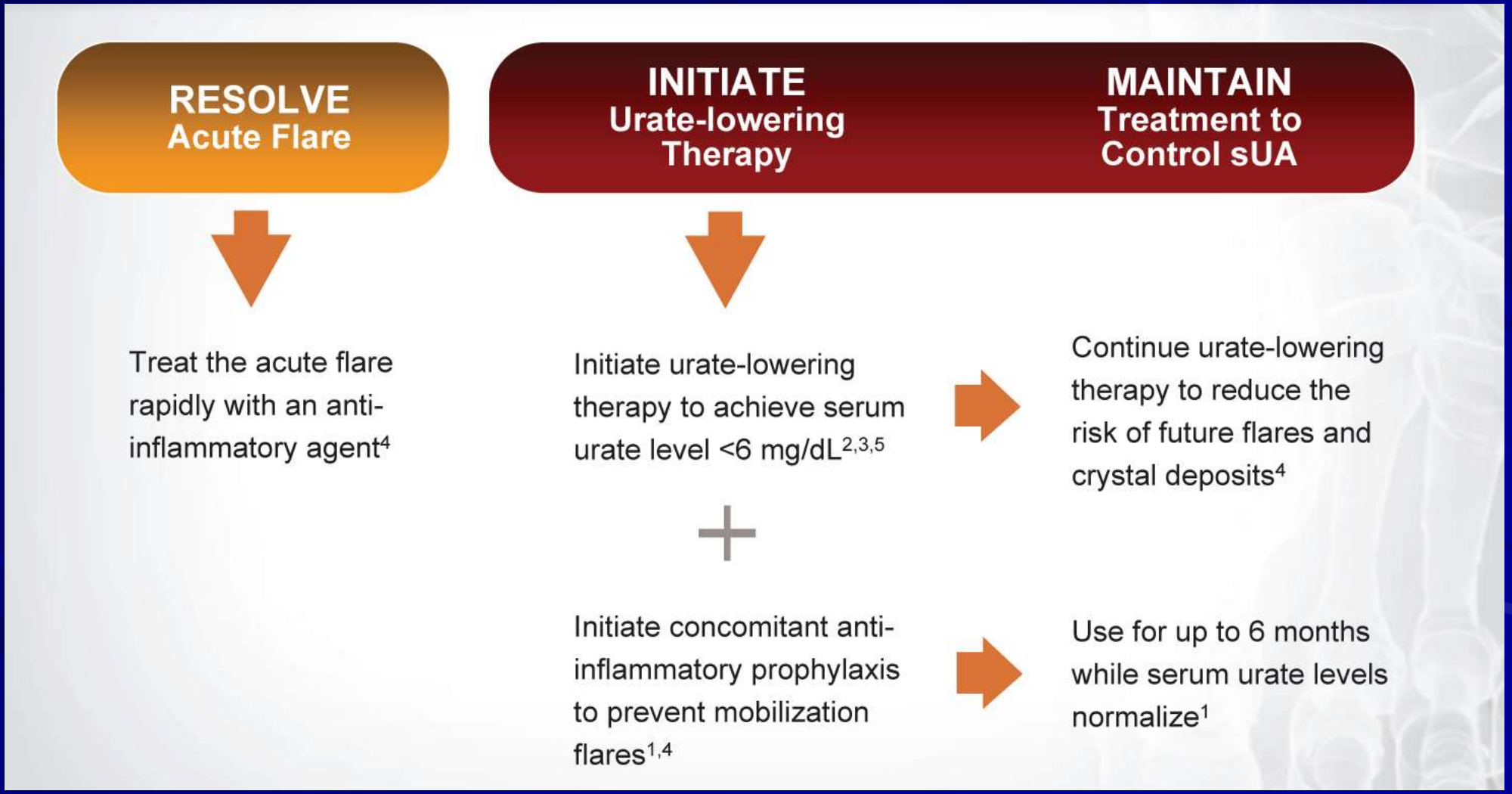
Patients

- Misunderstand causes of gout
- Don’t realize consequences of untreated gout
- May not view gout as a chronic disease
- Non-adherence to treatment plans
- Unwilling to adopt lifestyle modifications

Providers

- Only manage acute attacks rather than treat gout as a chronic progressive disease
- Lack urgency to treat
- Don’t adopt treat-to-target strategy
- Use only fixed doses
- No communication with patient’s other providers

Strategy for gout management



2012 ACR Gout Treatment Guidelines

Treat to Target

At minimum, sUA <6 mg/dL

or

sUA <5 mg/dL for those with chronic tophaceous gout

and

Durable improvement in signs and symptoms of gout

- Reduced frequency of flares
- Clearance of tophi

Urate-lowering therapy

Xanthine oxidase inhibitors
(Alternative if XOI contraindicated or not tolerated: probenecid)

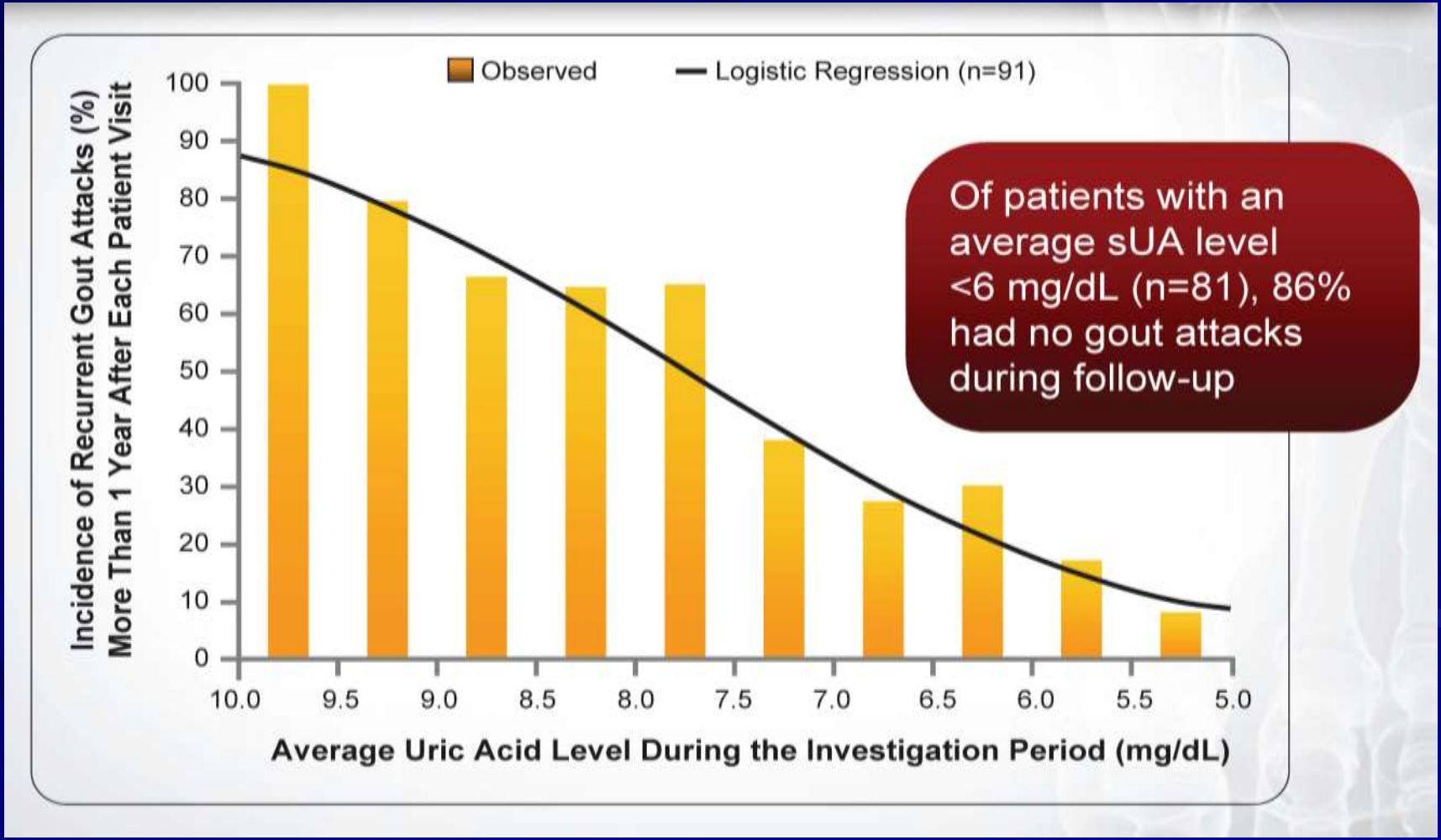
sUA target not achieved, continuing disease activity

Add uricosuric to XOI*

sUA target not achieved, continuing disease activity

Biologic therapy: pegloticase

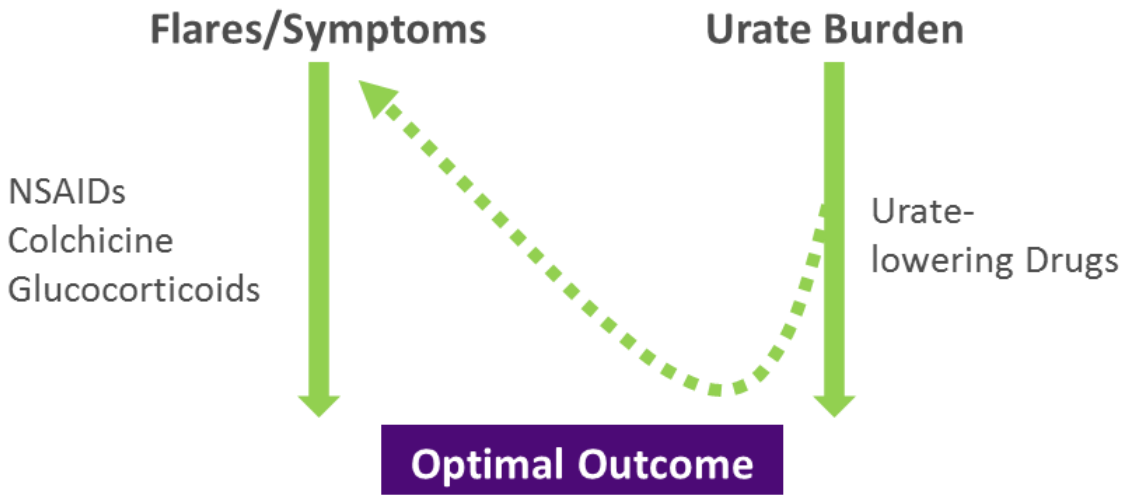
Maintaining sUA <6 mg/dL is associated with reduced risk of recurrent gout flares



Appropriate management of gout requires control of both symptoms and urate burden

Must address 2 processes simultaneously for successful outcomes:

- Control flares and symptoms
- Reduce urate burden



Adequate treatment of excess urate burden may lead to improvement in clinical manifestations[32]

Treatment of acute gout: Anti-inflammatories

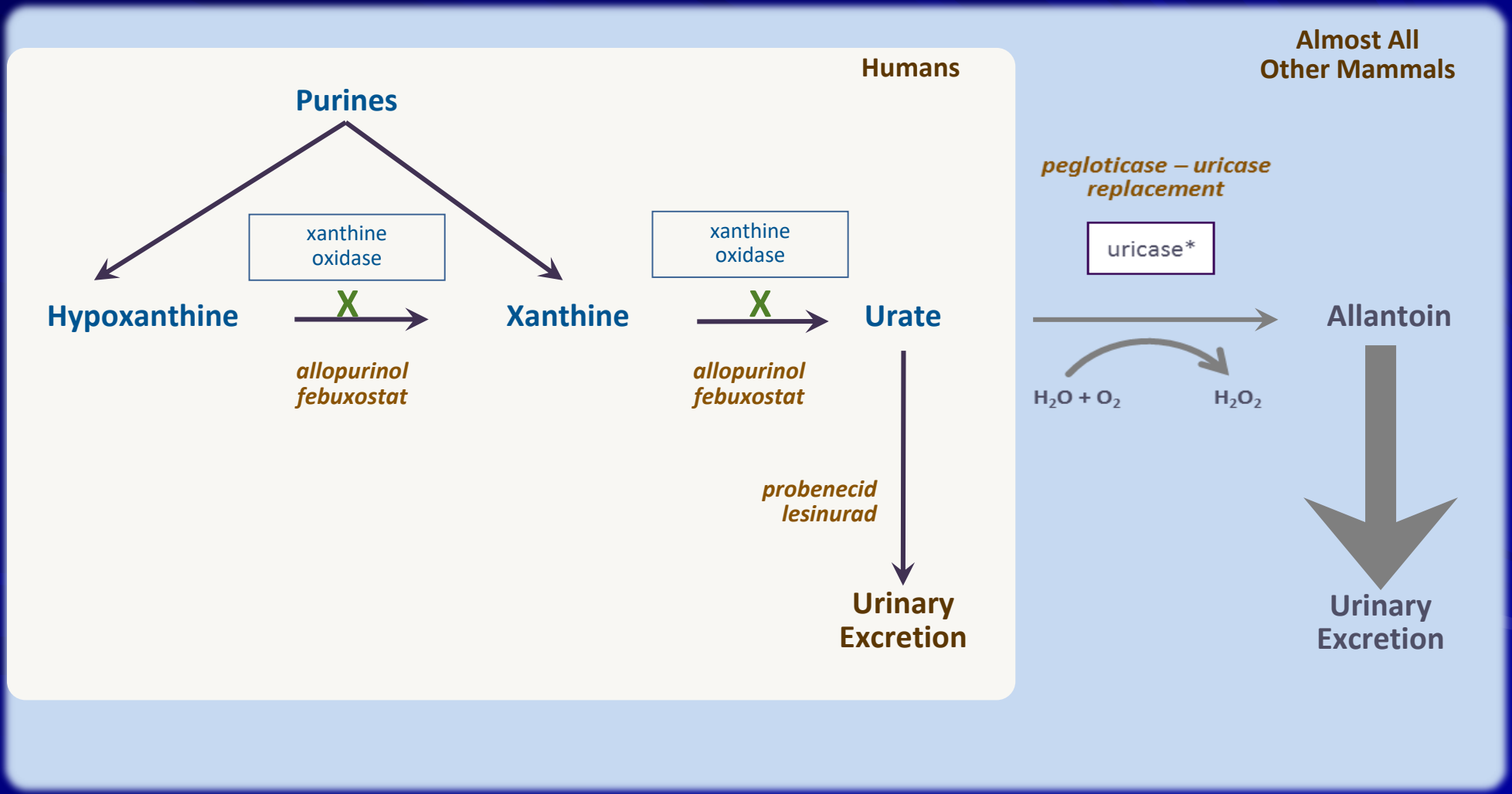
- NSAIDs
  - indomethacin: 75 mg three times daily
  - celecoxib: 200 mg twice daily
  - ibuprofen: 800 mg three times daily
  - naproxen 500 mg twice daily
- Colchicine: 1.2 mg at first sign, then 0.6 mg 1 hour later
- Steroids
  - Prednisone 20 mg daily x 4 d, 15 mg daily x 4 d, 10 mg daily x 4 d, 5 mg daily x 4 d.

Choice of therapy is dependent on patient's comorbidities

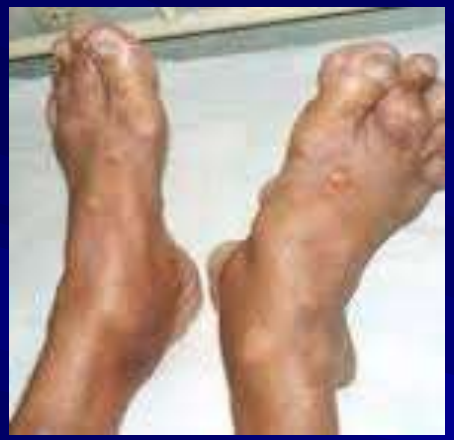
Treatment of chronic gout: Urate-lowering therapies (ULTs)

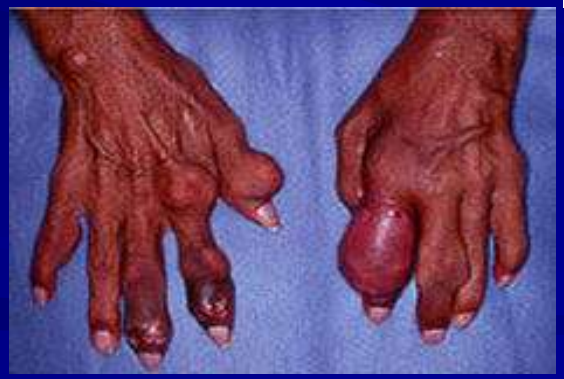
- Small molecules
  - xanthine oxidase inhibitors
    - allopurinol
    - febuxostat
  - combination XOIs and uricosurics
    - allopurinol / lesinurad
  - uricosurics
    - probenecid
    - lesinurad
- Biologics
  - uricase (pegloticase)

Purine catabolism



Management of refractory gout





Refractory gout: Definition

- Ongoing hyperuricemia or gout flares despite maximum appropriate doses of ULTs
  - Recurrent and disabling gout flares
  - Chronic gout arthropathy +/- bony erosions
  - Visible progressive tophi
  - Progressive physical disability
  - Poor health-related quality of life
- The combination of severe gout, comorbidities, and polypharmacy can make refractory gout challenging to manage

Treatment options for refractory gout

- Dose escalation of conventional urate lowering therapies:
  - allopurinol to 800 mg daily in divided doses
  - febuxostat to 160 – 240 mg daily
  - probenecid to 1000 mg daily in divided doses
  - lesinurad to 200 mg daily
- Combination therapy: xanthine oxidase inhibitor + uricosuric
- Lifestyle modifications
  - diet
  - exercise
  - cherry extract
  - vitamin C
  - losartan for diuretics
  - fenofibrate for niacin
  - avoidance of high fructose corn syrup
  - low fat dairy products
- Biologic therapy
  - pegloticase

Pegloticase: a biologic for the treatment of refractory gout

- pegloticase is recombinant modified porcine uricase surrounded by polyethylene glycol (PEG)
- PEG decreases immunogenicity and increases half-life of the molecule
- pegloticase catalyzes the break-down of uric acid to allantoin
  - allantoin is more water soluble than uric acid and is readily excreted by the kidneys, leading to lowering of sUA levels

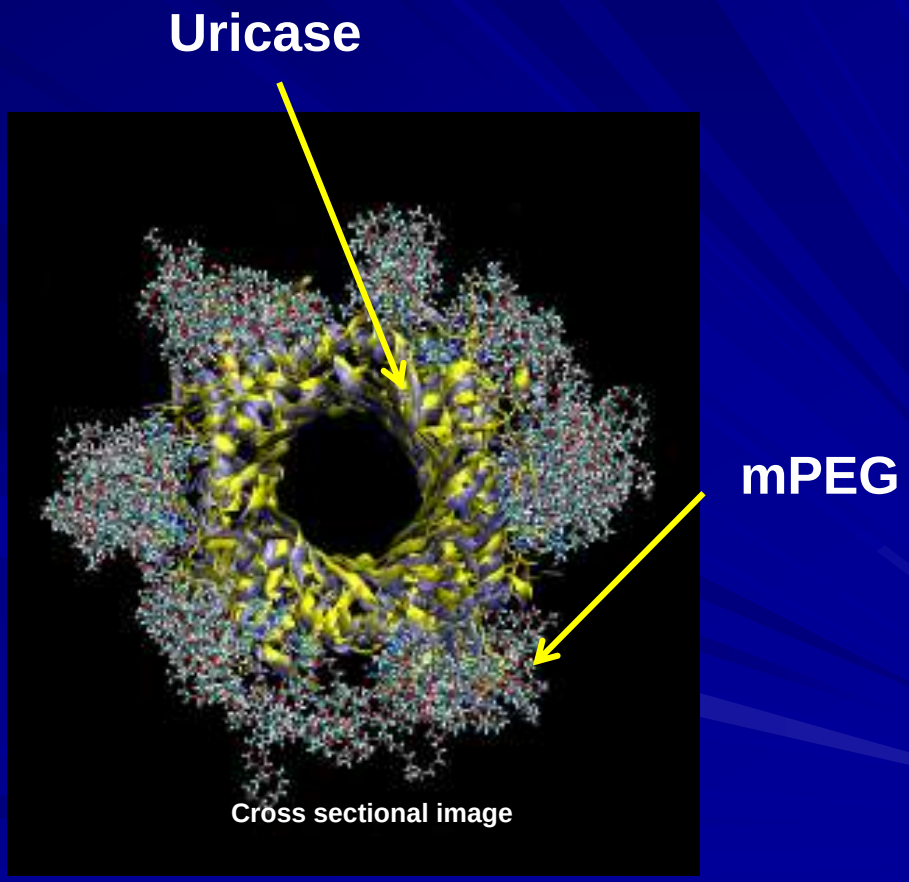
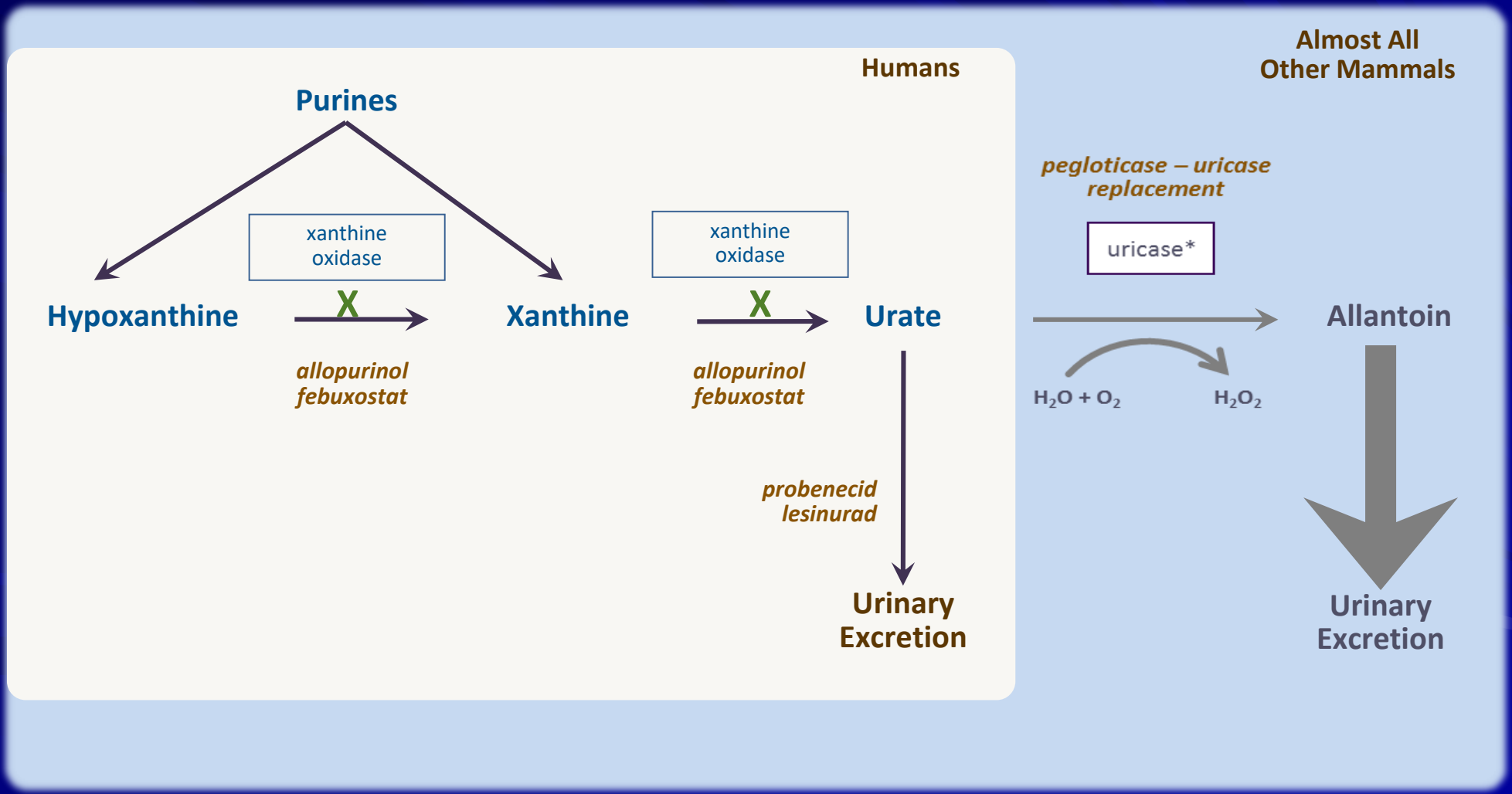


Figure courtesy of Toby Sannan and Christopher Hadad, Ohio State University.

Purine catabolism



Pegloticase: phase III trials

- Two replicate, multicenter, randomized, double-blind, placebo-controlled trials of 6 months' duration
  - Subjects included adults with chronic refractory gout
  - 8 mg pegloticase infusions every 2 weeks vs. placebo

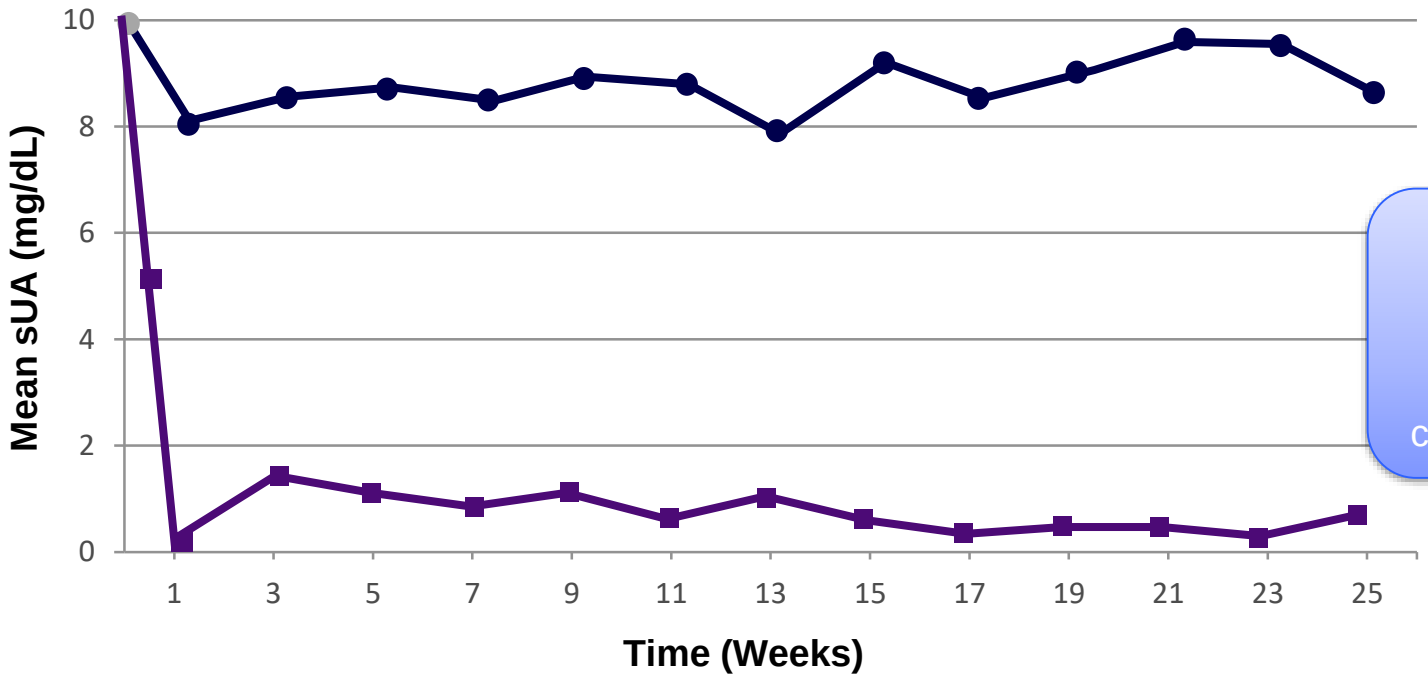
PRIMARY ENDPOINT

- Percentage of plasma uric acid (PUA) responders versus placebo
- **Complete Responders**
  - Patients who achieved PUA <6 mg/dL for 80% of the time during months 3 and 6
- **Incomplete Responders**
  - Patients who did not sustain PUA <6 mg/dL throughout the trial
  - Patients who withdrew before the final visit

SECONDARY ENDPOINT

- **Complete resolution (CR) of tophi**
  - Defined as 100% resolution of at least 1 target tophus, with no new or progressive tophi

Pooled trial results: Complete responders

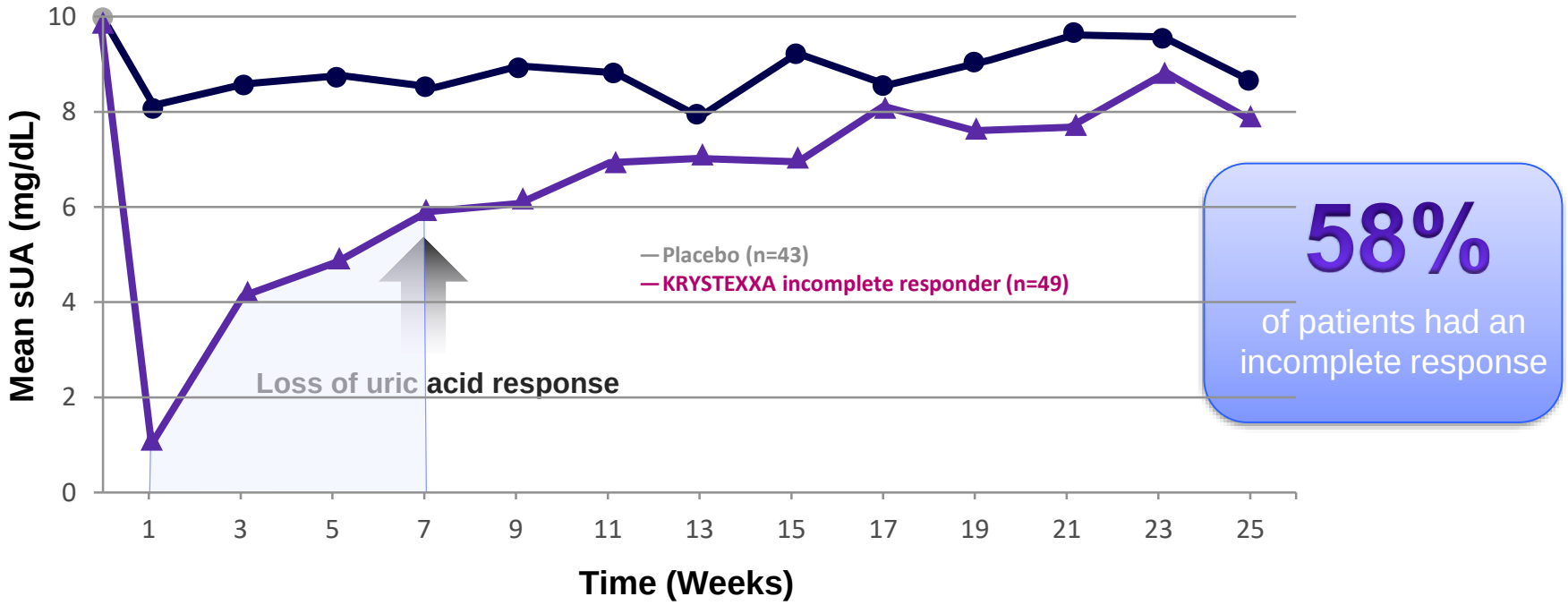


42%

of patients had a complete response

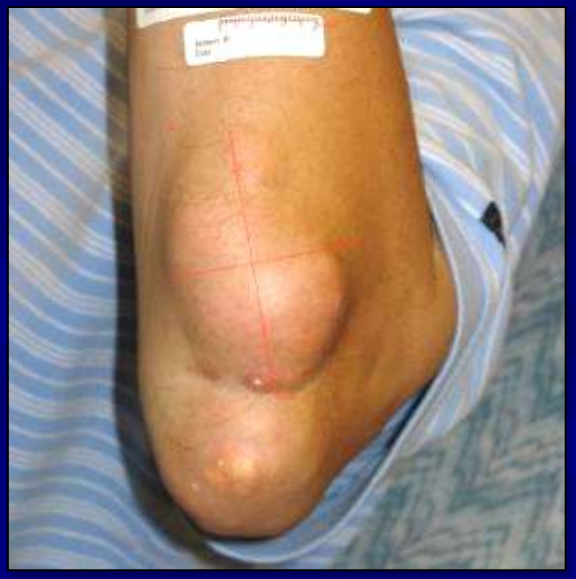
- These patients maintained sUA levels below 6 mg/dL 80% of the time at months 3 and 6 versus 0% for placebo (*P*<0.001)

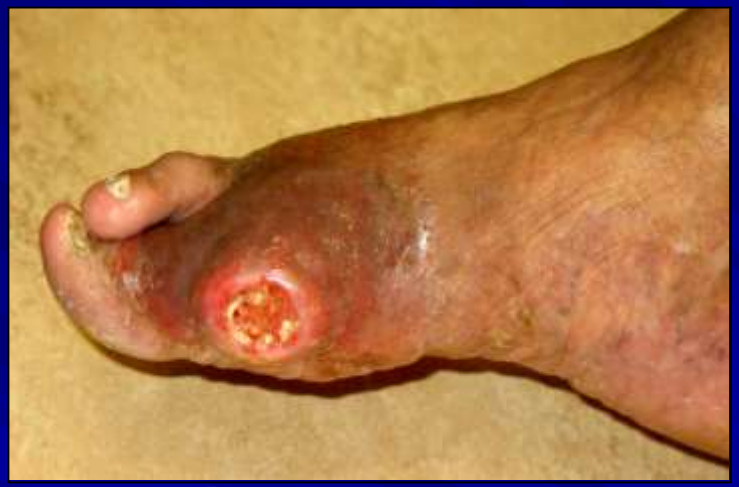
Pooled trial results: Incomplete responders



These patients achieved a reduction in sUA for a mean of 7 weeks, allowing some clearance of the urate burden ($P<0.001$). The response was not durable; therefore, they did not meet the primary endpoint.

Secondary endpoint: Tophus resolution

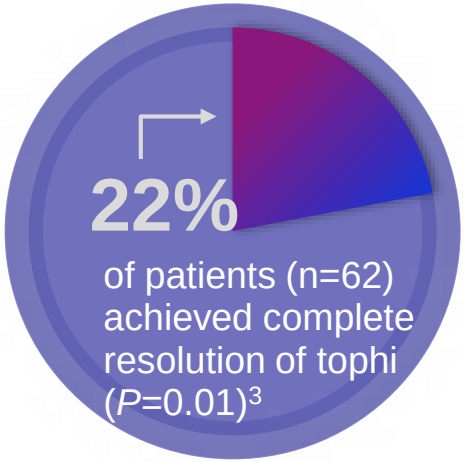




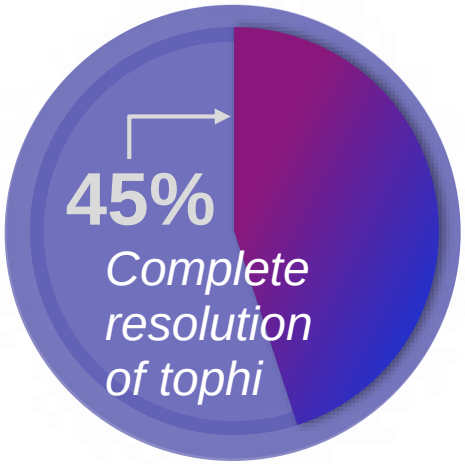
Secondary endpoint: Tophus resolution

Complete resolution of tophi
Defined as 100% resolution of at least 1 tophus, with no new or progressive tophi

3 Months



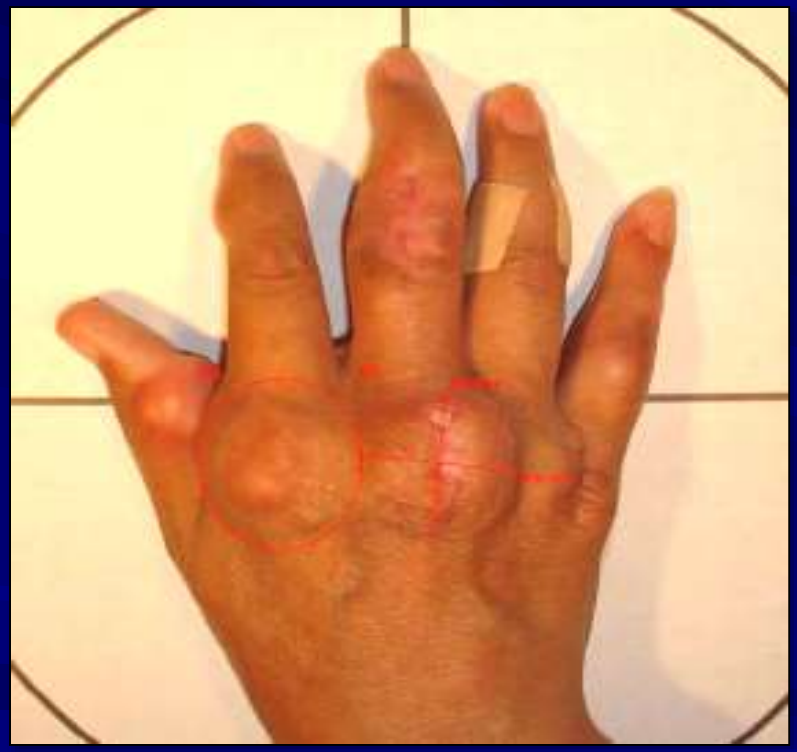
6 Months

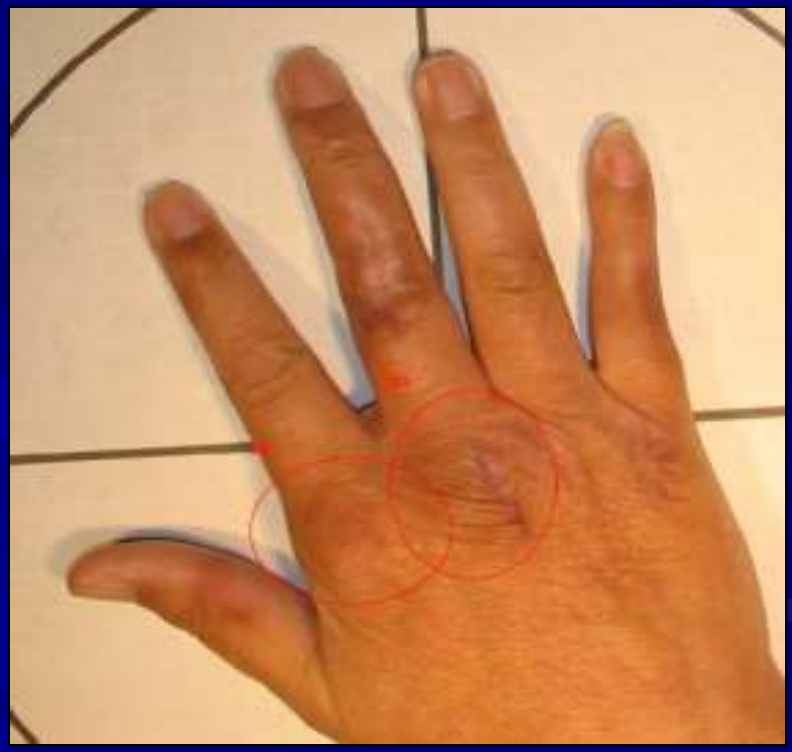


These results include patients who experienced a complete response as well as patients who experienced an incomplete response in the primary endpoint[3]

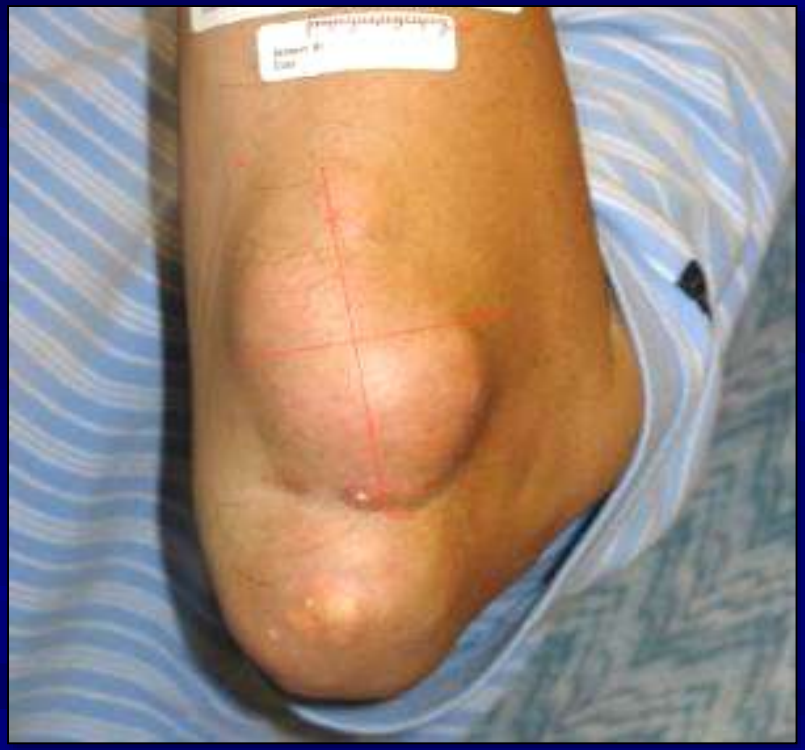
45% (18/40) of patients treated with pegloticase achieved complete resolution of their target tophus versus 8% (2/25) of patients receiving placebo (*P*=0.002)

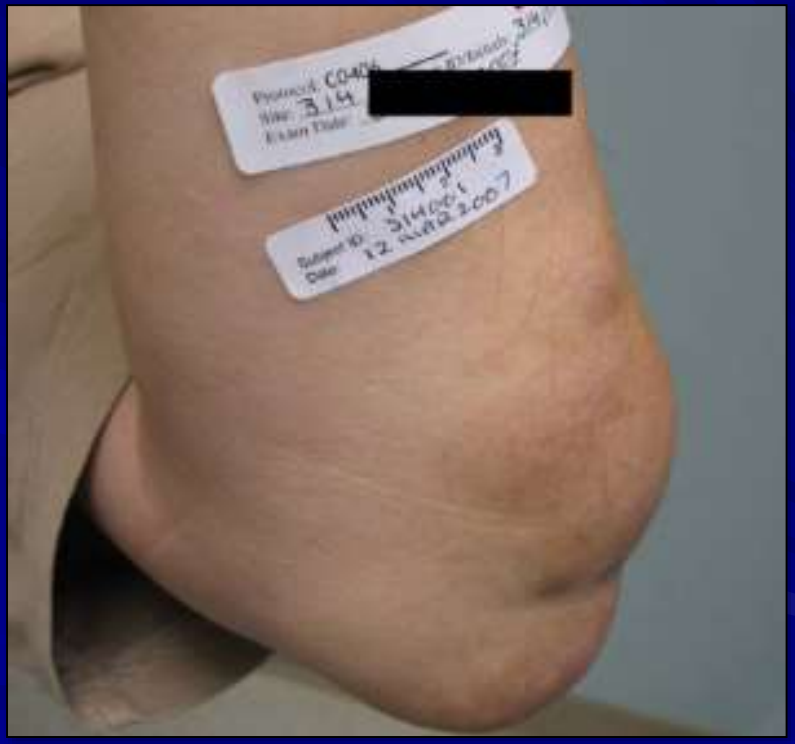
Secondary endpoint: Tophus resolution



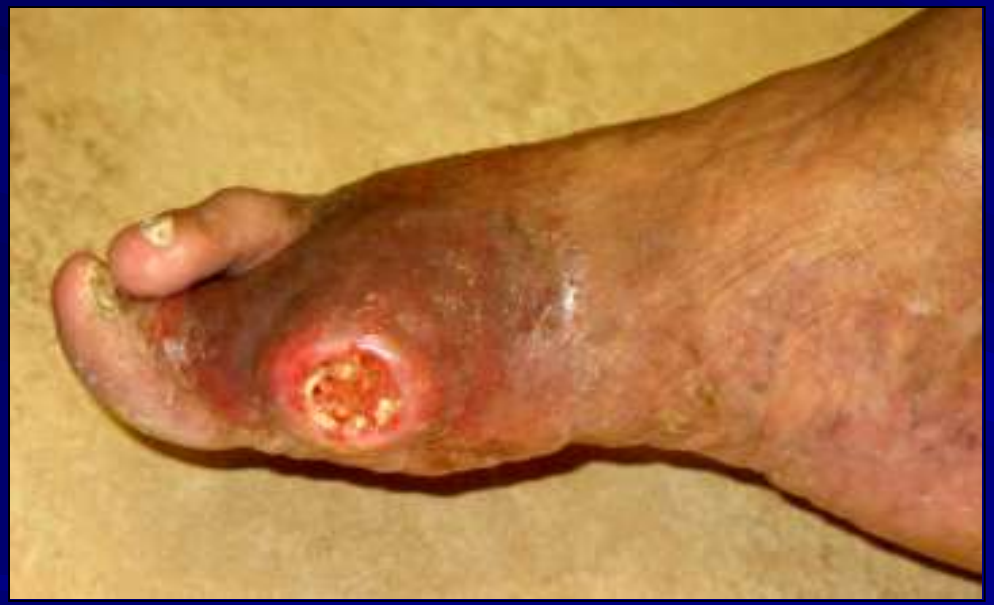


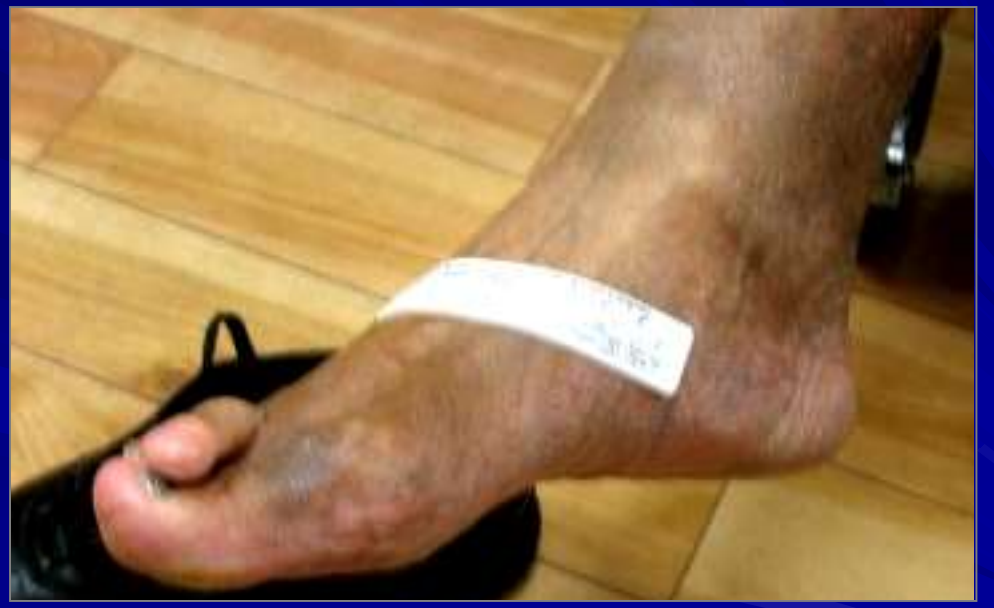
Secondary endpoint: Tophus resolution





Secondary endpoint: Tophus resolution





Safety: Adverse events

- Most common adverse events (occurring >5% of patients)
  - Gout flares
  - Infusion reactions
  - Nausea
  - Vomiting
  - Contusion or ecchymosis
  - Nasopharyngitis
  - Constipation
  - Chest pain

Adverse events: Infusion reactions

- Most infusion reactions (IRs) occurred when sUA levels were >6 mg/dL (91% vs 4.5%)
- If sUA levels increase to >6 mg/dL on therapy, patient is likely to have anti-pegloticase antibodies, and may be at increased risk of infusion reactions
- If pegloticase is discontinued after the sUA >6 mg/dL, most IRs could be avoided

Using sUA as a predictive biomarker: Stopping rule

- Check a sUA 48 hours before each pegloticase infusion:
  - If SUA <6 mg/dL, infusion can be given
  - If SUA >6 mg/dL, consider discontinuing treatment, particularly when 2 consecutive sUA levels >6 mg/dL are observed
- If this stopping rule is utilized, the majority of infusion reactions can be avoided
- No other biologic in Rheumatology has a predictive biomarker

Safety: Pre-infusion protocol

Infusion pre-medications

- Antihistamine the night before and the morning of each infusion
- Acetaminophen the morning of the infusion
- Corticosteroids prior to each infusion

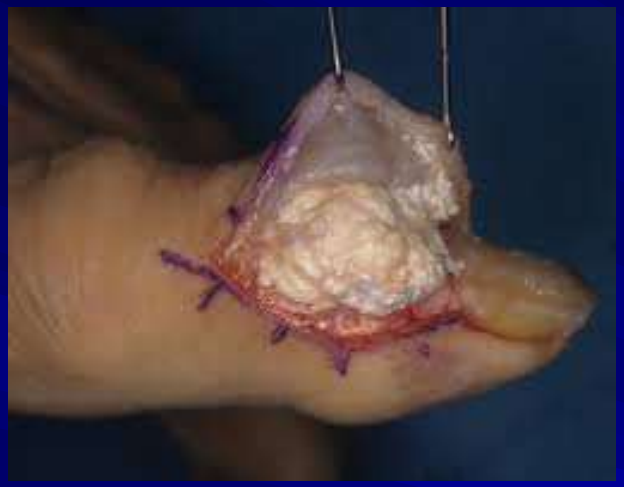
Gout flare prophylaxis

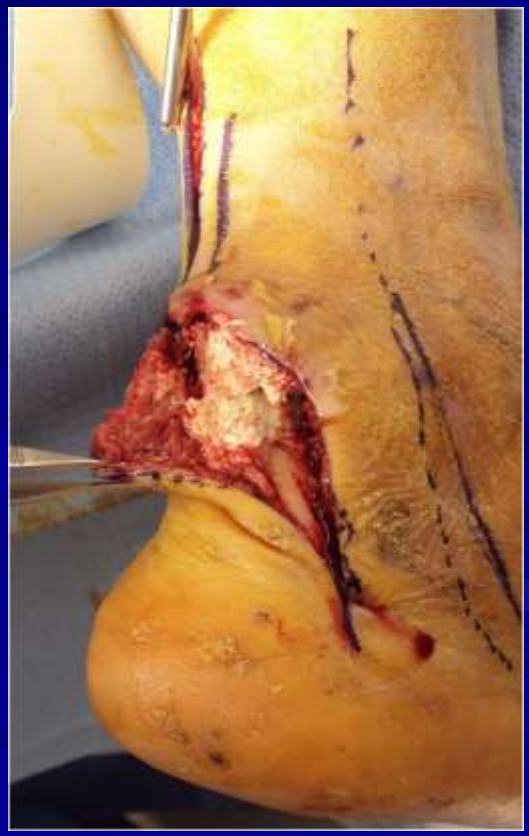
- Colchicine, NSAIDS, or both
- Initiate 1 week before starting pegloticase
- Continue for at least 6 months

Oral urate-lowering therapy

- Discontinue any oral ULT the day before starting pegloticase to prevent confounding of the sUA predictive biomarker effect
- May reinitiate once pegloticase course is completed

Perioperative management of the gout patient





Perioperative considerations

- Gout has many associated comorbidities:
  - hypertenstion
  - coronary heart disease
  - congestive heart failure
  - atrial fibrillation
  - diabetes mellitus
  - hyperlipidemia
  - chronic kidney disease
  - peripheral vascular disease
- Appropriate medical clearance should be obtained prior to any surgical intervention
- Post-operative gout flares are common

Perioperative management

- Optimize ULT preoperatively
  - Risk of gout attacks decreases if sUA <6 mg/dL
- Maintain ULT until NPO status on day of surgery
  - Reinitiate as soon as appropriate postoperatively
- May consider short prophylactic course preoperatively
  - Low-dose NSAIDs or colchicine 0.6 mg QD/BID
- If gout flares postoperatively, treat with anti-inflammatories
  - High-dose NSAIDS, colchicine, or steroids

Summary

- Gout is a chronic, progressive arthritis caused by hyperuricemia with associated chronic inflammation
- Podiatrists play a critical role in the management of gout
- Collaboration between podiatrists and rheumatologists can lead to optimal care of the gout patient
- Appropriate treatment of gout includes treating acute flares with anti-inflammatories AND treating the underlying hyperuricemia with urate-lowering therapies

Summary

- Treatment for acute gout flares include NSAIDs, colchicine, and steroids
- ULTs include xanthine oxidase inhibitors (allopurinol, febuxostat), uricosurics (probenecid, lesinurad), combination therapies, and biologics (pegloticase)
- Pegloticase is the first biologic and only FDA-approved treatment option for patients with refractory gout
- Optimization sUA <6 mg/dL preoperatively reduces risk of gout flares postoperatively

Questions???

Thank You !

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