Update on Gout

New trends for a very old disease

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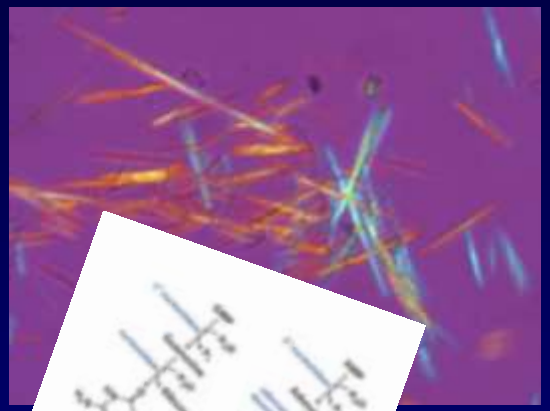
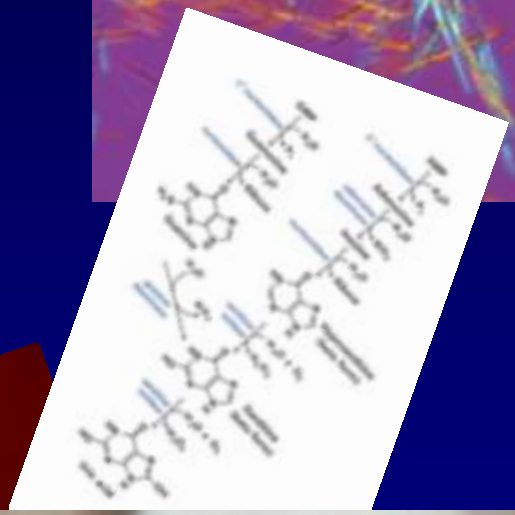
Disclosures

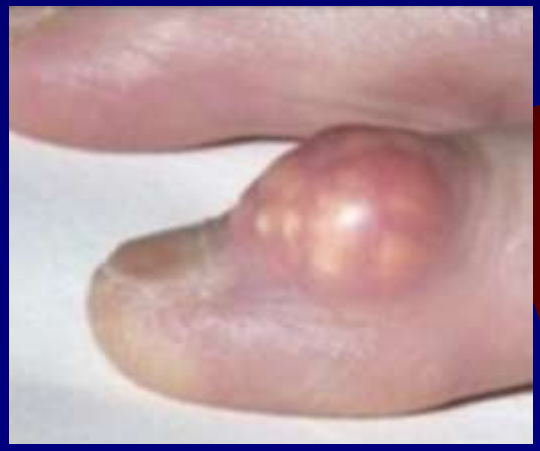
- Investigator, CSP594 Stop Gout trial

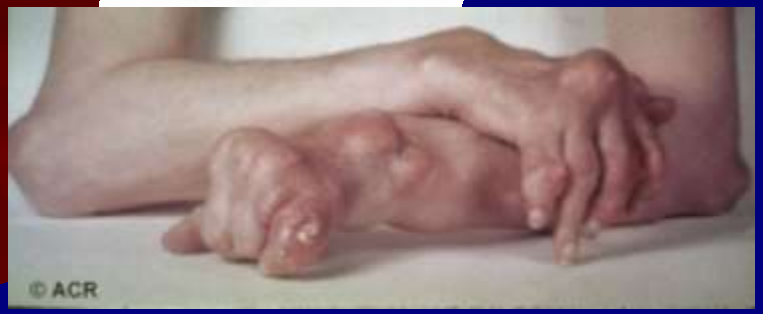
Gout

- Colorful
- Well understood
- Enigmatic
- Continually challenging









Learning Objectives for Gout

- Understand management goals
- Recognize management challenges
- Understand benefits of ULT
- Appreciate new treatment targets
- Review current treatment guidelines

ULT = urate lowering therapy

Gout is Common

- Most common cause of inflammatory arthritis in men
- Associations: CKD, HTN, obesity, DM, (metabolic syndrome), CVD, renal stones, CPPD
- Risk Factors: age, serum uric acid, CKD, obesity, alcohol, diet, medications, genetics.

A Colorful History

Rodnan Gout Prints, ACR Rheumatology Research Foundation

Field Museum, Chicago

Prevalence

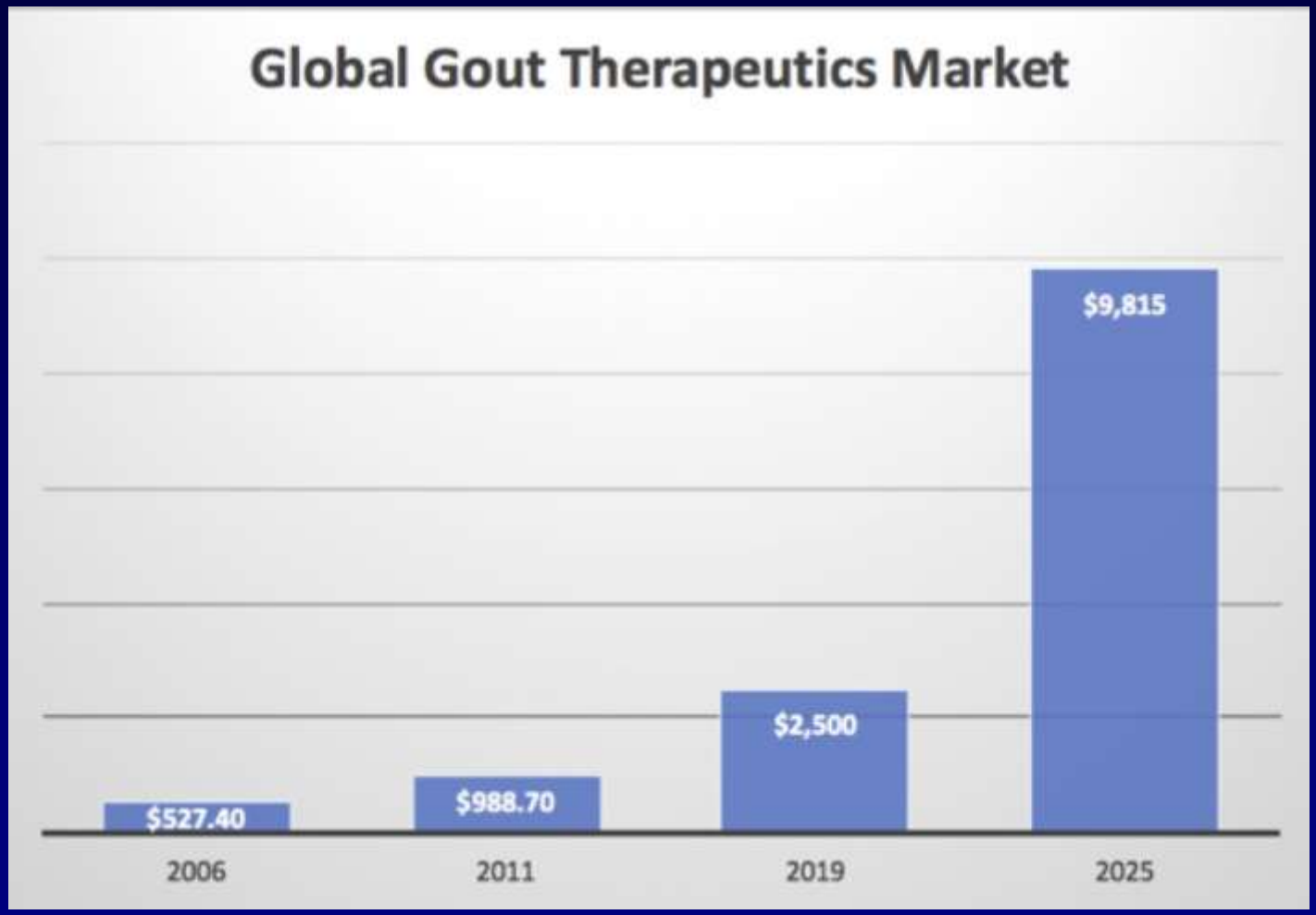
Table 3. Unadjusted and age-adjusted comparison of the prevalence of gout and hyperuricemia among US adults between NHANES-III (1988–1994) and NHANES 2007–2008 *

	NHANES-III	NHANES 2007–2008	Difference
Prevalence of gout			
Unadjusted	2.7 (2.3, 3.0)	3.9 (3.3, 4.4)	1.2 (0.6, 1.9)
Age-adjusted	2.9 (2.5, 3.3)	3.9 (3.4, 4.5)	1.0 (0.4, 1.7)
Prevalence of hyperuricemia			
Unadjusted	18.2 (17.2, 19.3)	21.4 (19.7, 23.2)	3.2 (1.2, 5.2)
Age-adjusted	19.1 (18.1, 20.0)	21.5 (20.1, 23.0)	2.4 (0.7, 4.2)
Mean serum urate level, mg/dl			
Unadjusted	5.33 (5.29, 5.37)	5.48 (5.41, 5.55)	0.15 (0.07, 0.24)
Age-adjusted	5.36 (5.32, 5.40)	5.49 (5.44, 5.53)	0.13 (0.07, 0.18)

* Values are the percent (95% confidence interval). The data were adjusted for clusters and strata of the complex sample design of the National Health and Nutrition Examination Survey (NHANES) 2007–2008, with incorporation of sample weights.

Zhu Y, , et al., Arthritis and Rheumatology, 63:3136-41, 2011

Now it's big business…



GlobalData, Polaris

Gout is a disease of hyperuricemia

- Saturation concentration of urate in serum at 37^{o}C. is 7.0 mg/dl
- Serum uric acid >8.0 in Men
  >7.0 in Women is ABnormal

Framingham Data (12 yr f/u)

Urate Level (mg/dl)	Occurrence of Gout (%)
Less than 7	2
7-8	17
8-9	25
9 or greater	83

Natural History of Disease

Asymptomatic Hyperuricemia

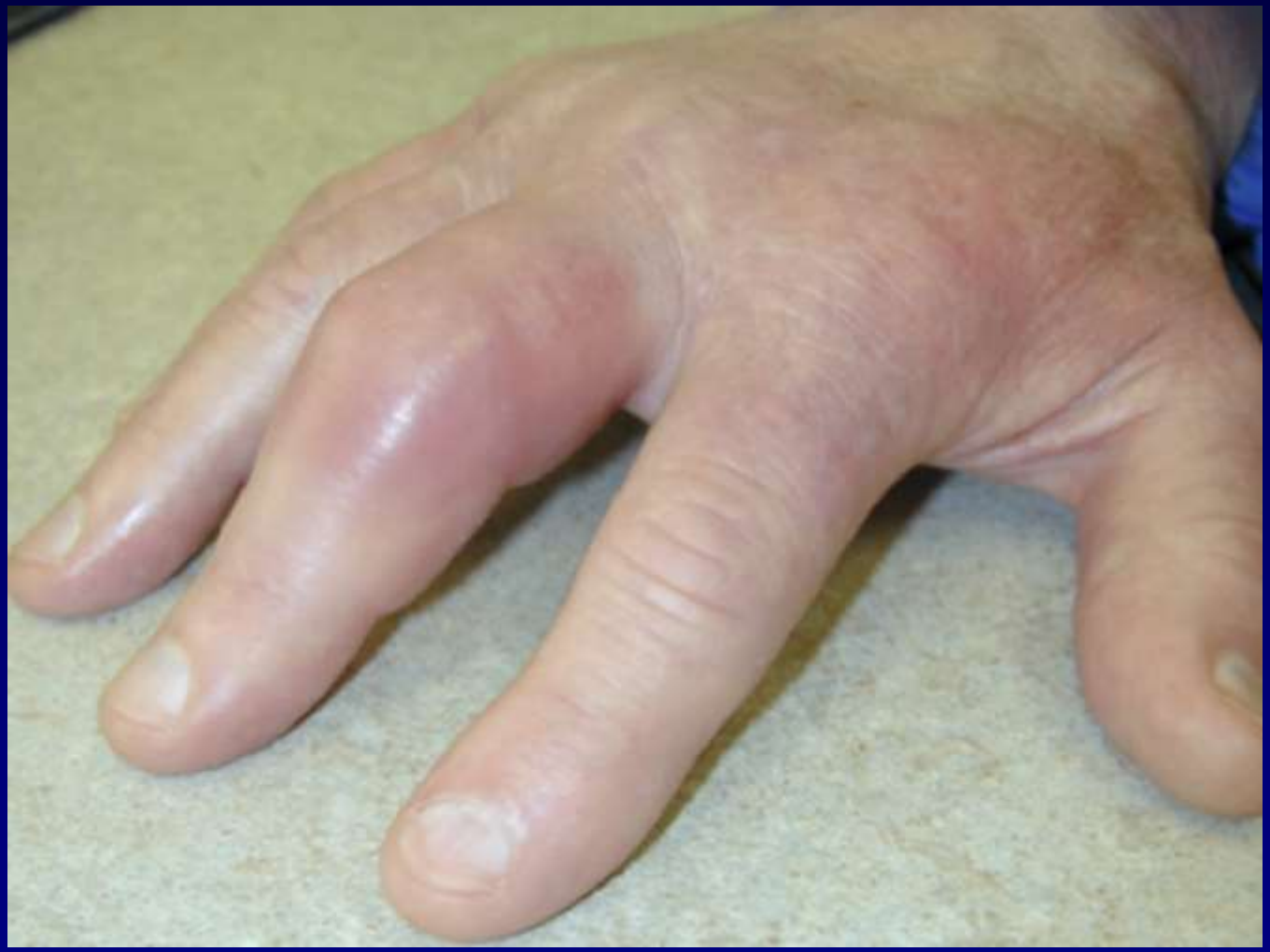
Acute Gout

Intercritical Gout

Recurrent Attacks

Chronic (Tophaceous) Gout

Acute Gout



Gout (in the classic form) is easily diagnosed

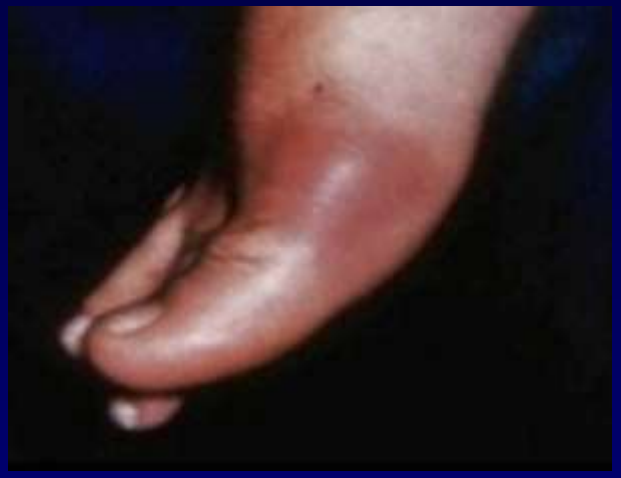
- An acute inflammatory arthritis that most commonly affects a single joint.
- Rapid onset of pain and inflammation (within 24 hrs.).
- Attacks are separated by intercurrent periods that are completely asymptomatic.
- Once a single attack has occurred, there is a 50% recurrence rate within the first year.

Acute Gout - Clinical Features

- Rapid development of monoarticular or oligoarticular pain, tenderness and inflammation
- Inflammatory synovial fluid
  - cloudy to purulent
  - >40-50,000 wbc
  - neutrophil predominance (90%)
- Serum uric acid is unreliable in setting of acute attack
- Attacks self-limit, generally within 7-10 days
- May occur in polyarticular form

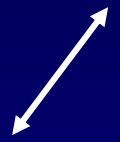
Differential Dx of Podagra

- ST Infection
- Septic arthritis
- Bunion
- Trauma
- Septic embolus
- SNSA (Reactive arthritis/PsA Arthritis)
- Calcific periarthritis (tendinitis)
- CPPD “pseudogout”

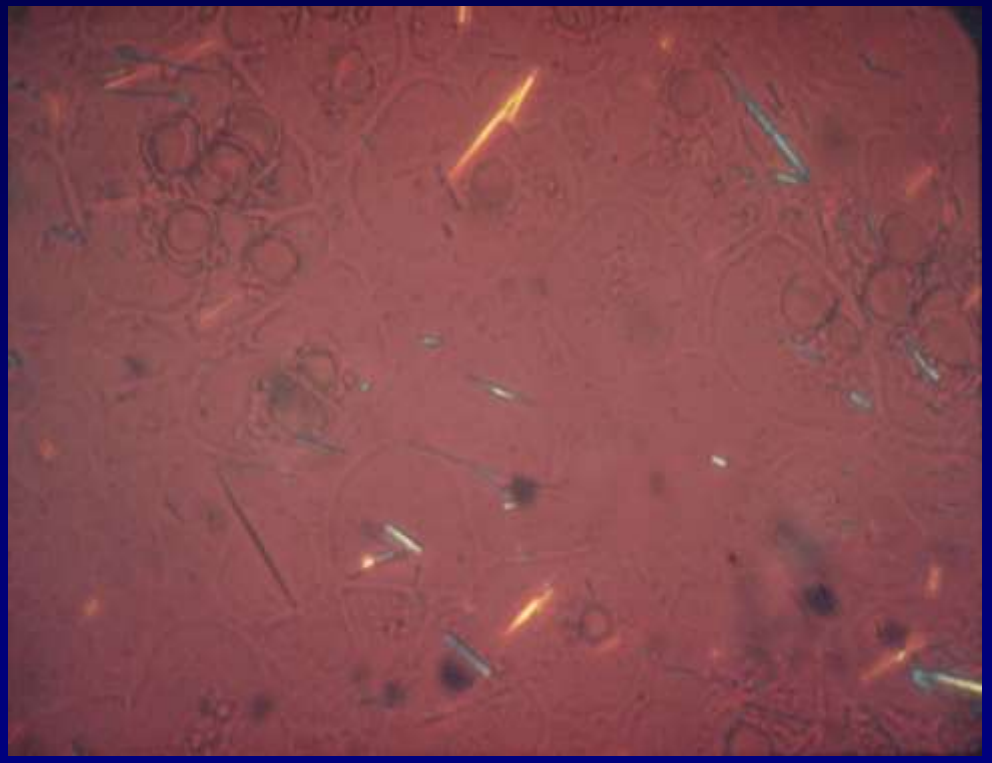


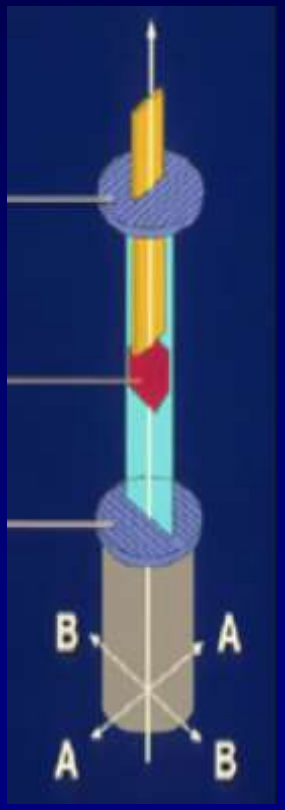
Diagnosis of Gout

- Aspiration of synovial fluid
- Demonstration of needle-shaped crystals with negative birefringence on polarized compensated microscopy



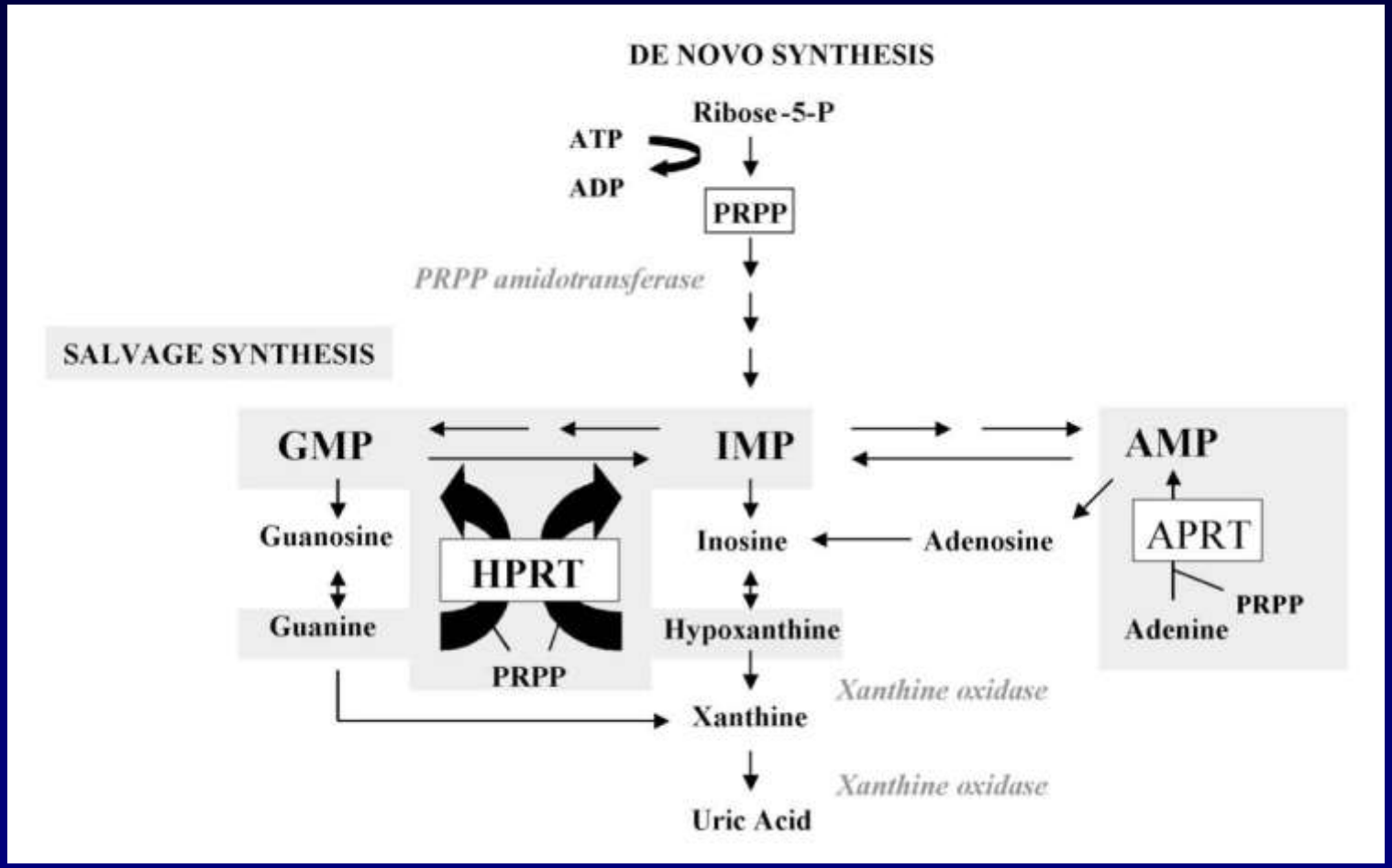
Orientation
Of Polarizer





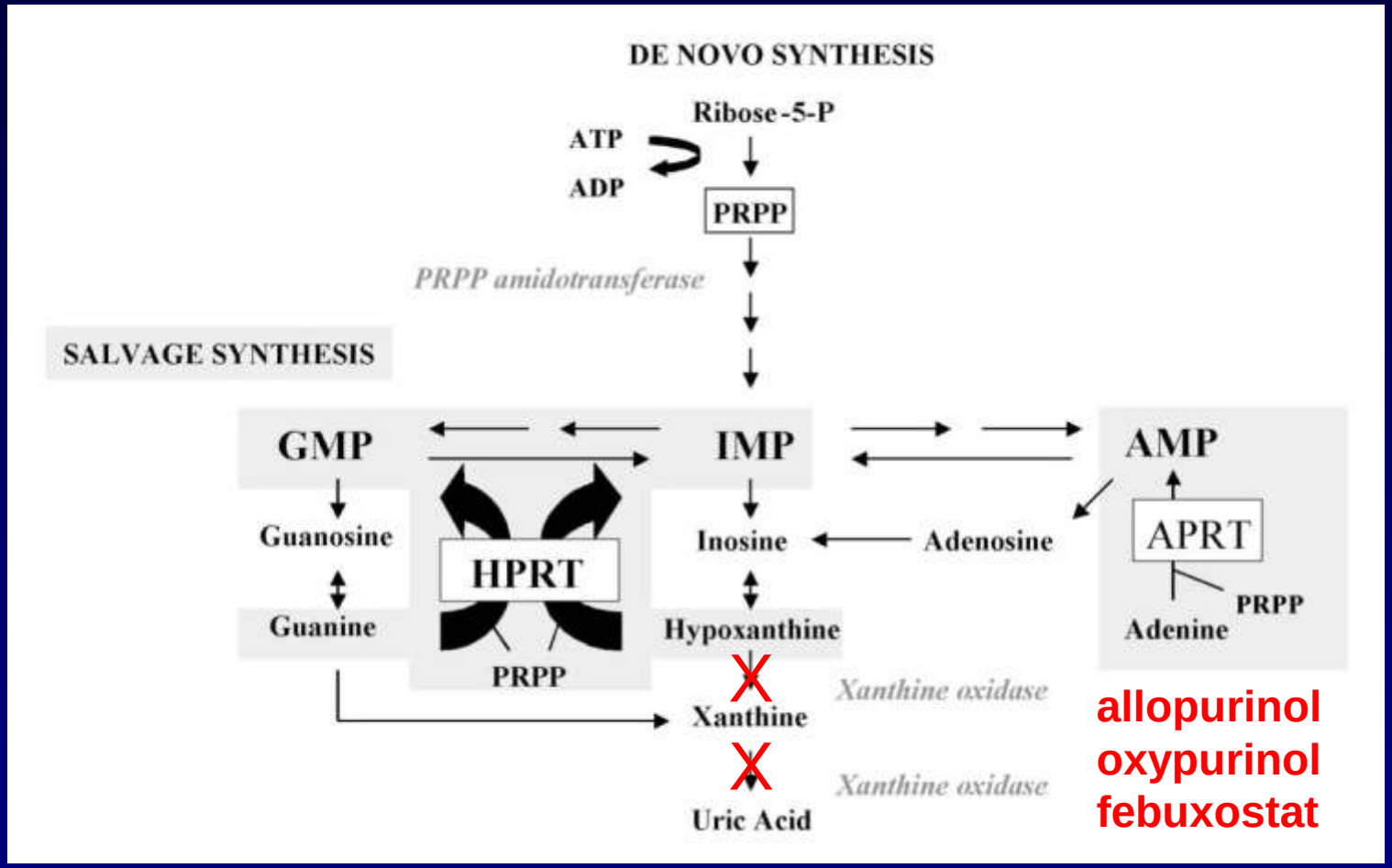
Yellow = Parallel

Pathogenesis of Gout



Torres RJ, Puig JG. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency: Lesch-Nyhan Syndrome. Orphanet J Rare Dis. 2, 1. 2007. WikiMEdia Commons HPRT Metabolism.

Pathogenesis of Gout

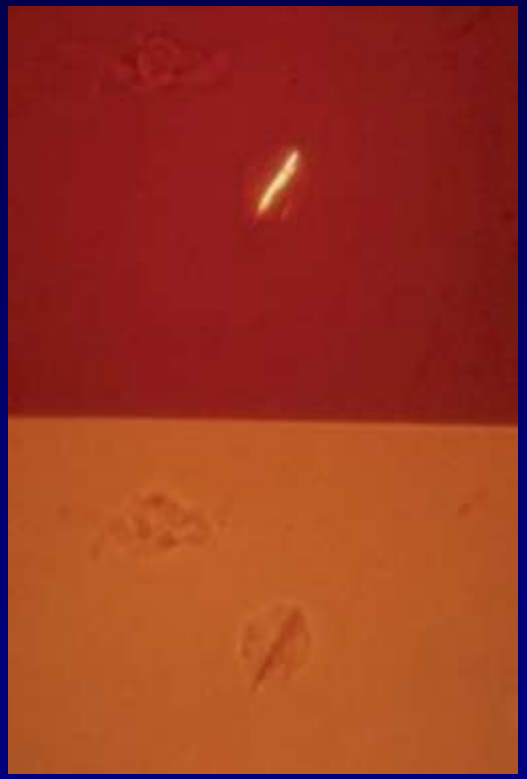


Torres RJ, Puig JG. Hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency: Lesch-Nyhan Syndrome. Orphanet J Rare Dis. 2, 1. 2007. WikiMEdia Commons HPRT Metabolism.

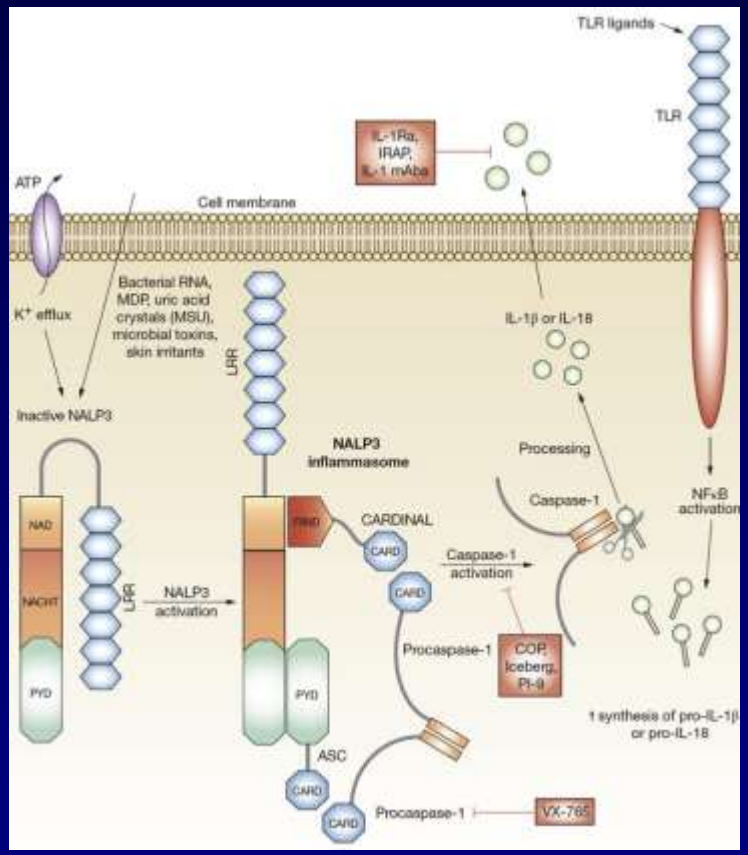
Pathogenesis of Gout

Pathogenesis

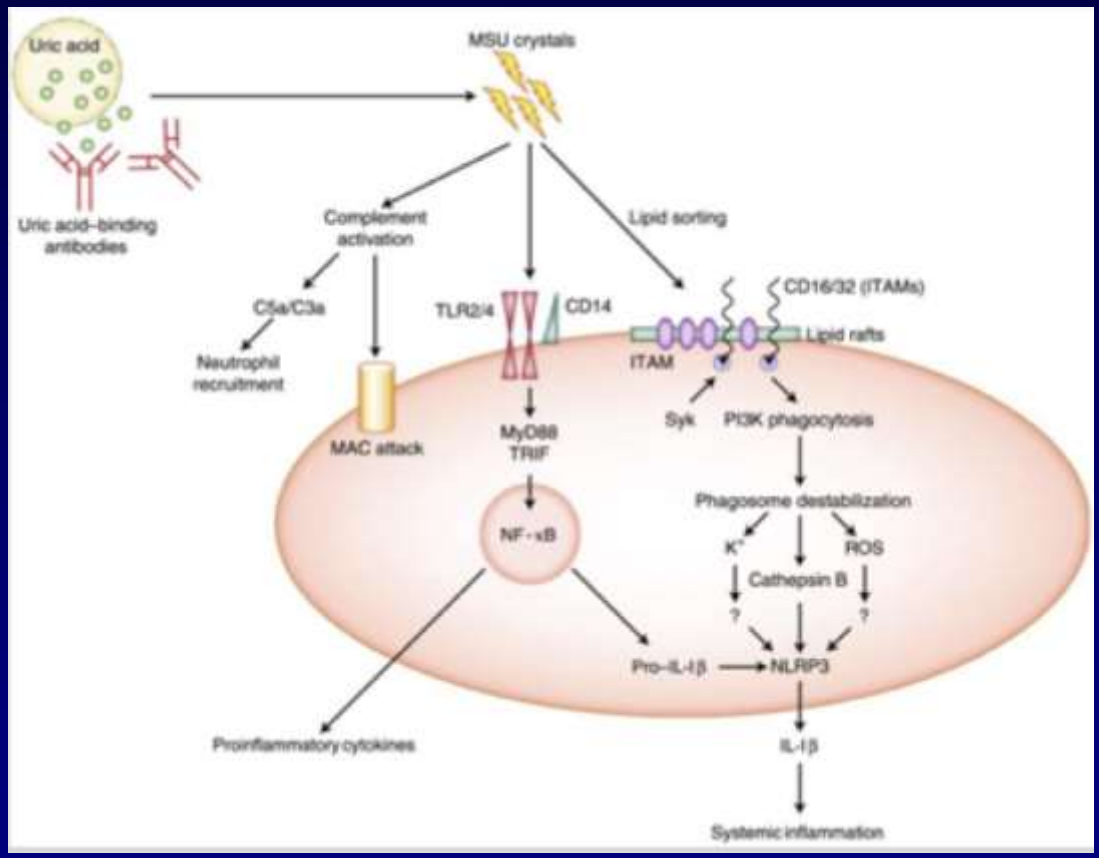
- Immunoglobulin-coated crystals contained by synovial monocytes and macrophages.
- MSU crystals results in activation of an innate immune response.
- Resulting neutrophil infiltration of joint is the hallmark of gouty inflammation.



Induction of IL1β via the NALP3 Inflammasome



Church LD, et al.,Nature Clinical Practice, 4:2008



Ghaemi-Oskouie F, Shi Y, Curr Rheumatol Rep, 13:160, 2011

Anakinra for the treatment of acute gout flares

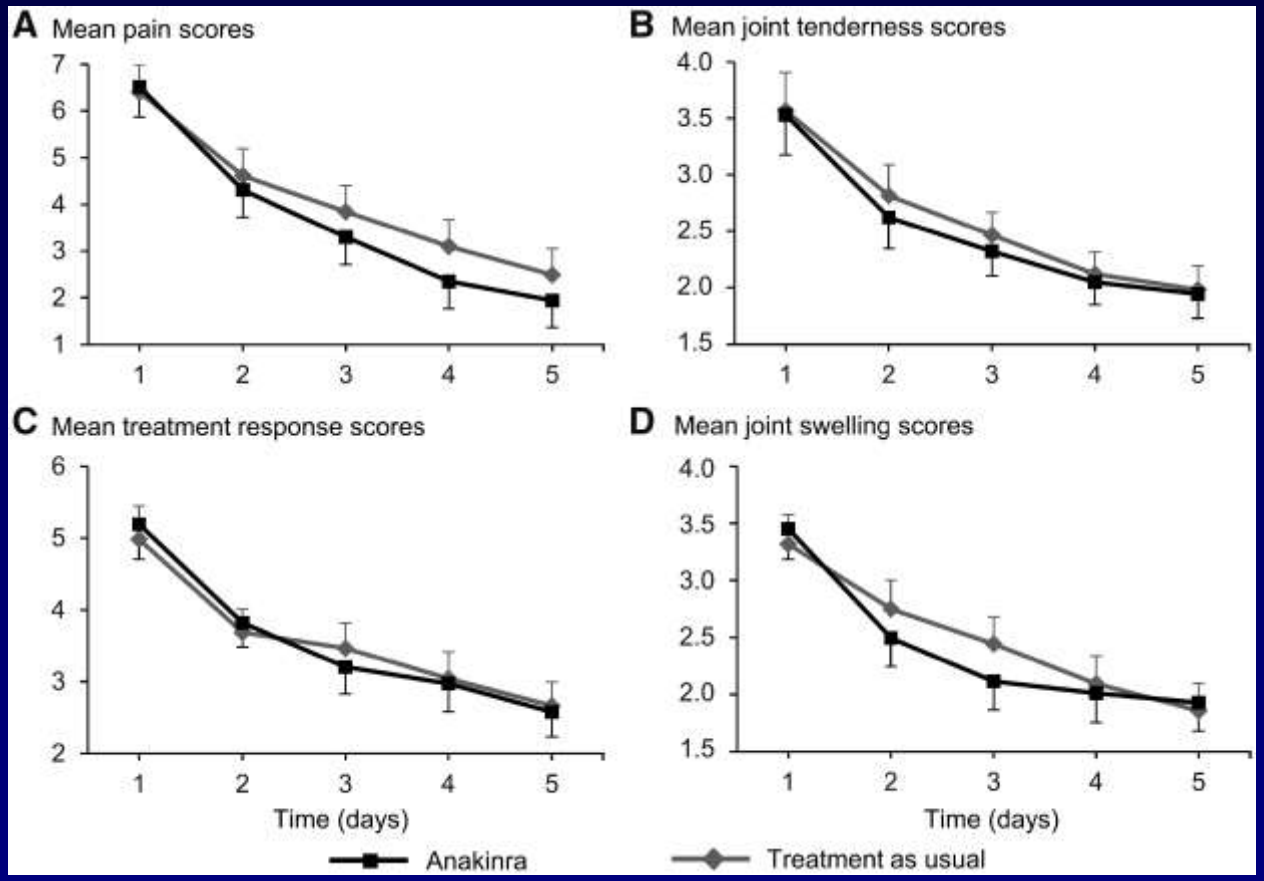


Fig. 3 Mean scores on days 1–5 (bars represent one-sided 95% CI) of the secondary outcomes (panel A–D)

Janssen CJ, et al., Rheumatology, Volume 58, Issue 8, August 2019, Pages 1344–1352

Treatment of Acute Gout

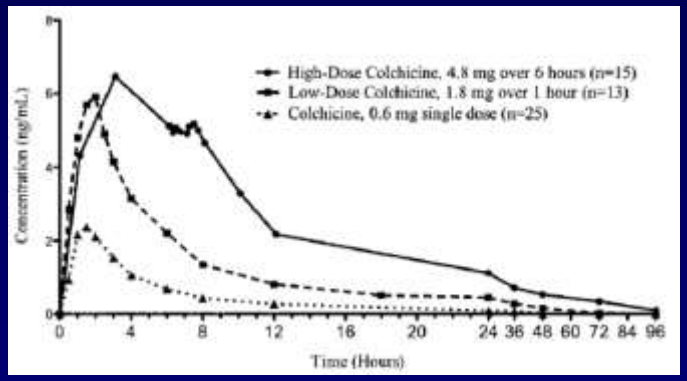
- NSAIDs
  - Indocin is historical preference
  - All NSAIDS have similar efficacy
- Corticosteroids
  - Intra-articular
  - Oral prednisone in moderate doses
- Oral Colchicine
  - Only effective if started within first 24 -48 hrs of an attack
  - Historical Approach - 1 po q hr until diarrhea

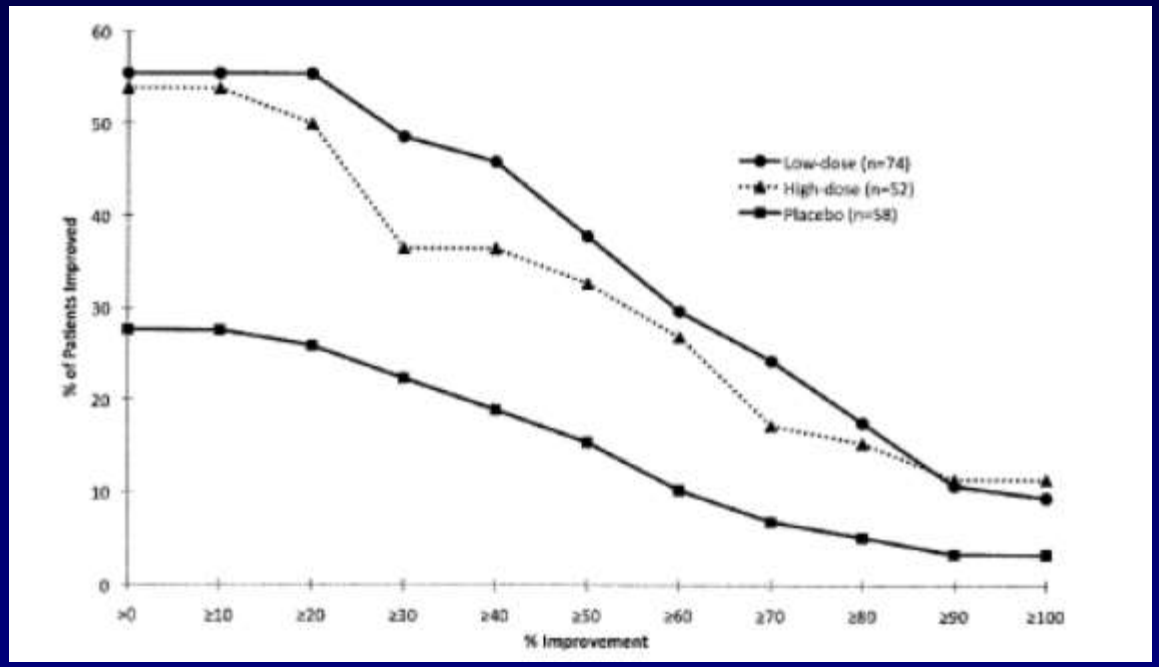
    "Patients often run before they walk"
- Anakinra

AGREE Trial of Colchicine for Acute Gout

"Low-Dose " 1.8 mg over 1 hr (1.2 + 0.6)

"High Dose" 4.8 mg over 6 hrs (1.2 + 0.6/hr)





	Rescue Med (%)	Diarrhea (%)
Placebo	50.0	13.6
LD	31.1	23.0
HD	34.6	76.9

Terkletaub RA, et al., A&R 62:1060-1068, 2010

Colchicine

Colchicum autumnale

- Useful for acute treatment and prophylaxis
- Reversible microtubule inhibitor
- Inhibits NALP3 inflammasome activation
- Now an expensive medication

Colcrys – a modern tragedy

- Oral colchicine used for decades
- 2006 - FDA Unapproved Drugs safety Initiaive
- URL Pharma did 17 dosing and safety studies
  - $100 million investment, $45 million to FDA
- 2009 - Received exclusive labeling for acute gout, gout prophylaxis and FMF
- FDA removed unapproved colchicine from market
- URL Pharma raised tablet price from $0.09 to $4.85
- 2012 - Takeda purchased URL for $800 million and immediately generated $1.2 billion in revenue

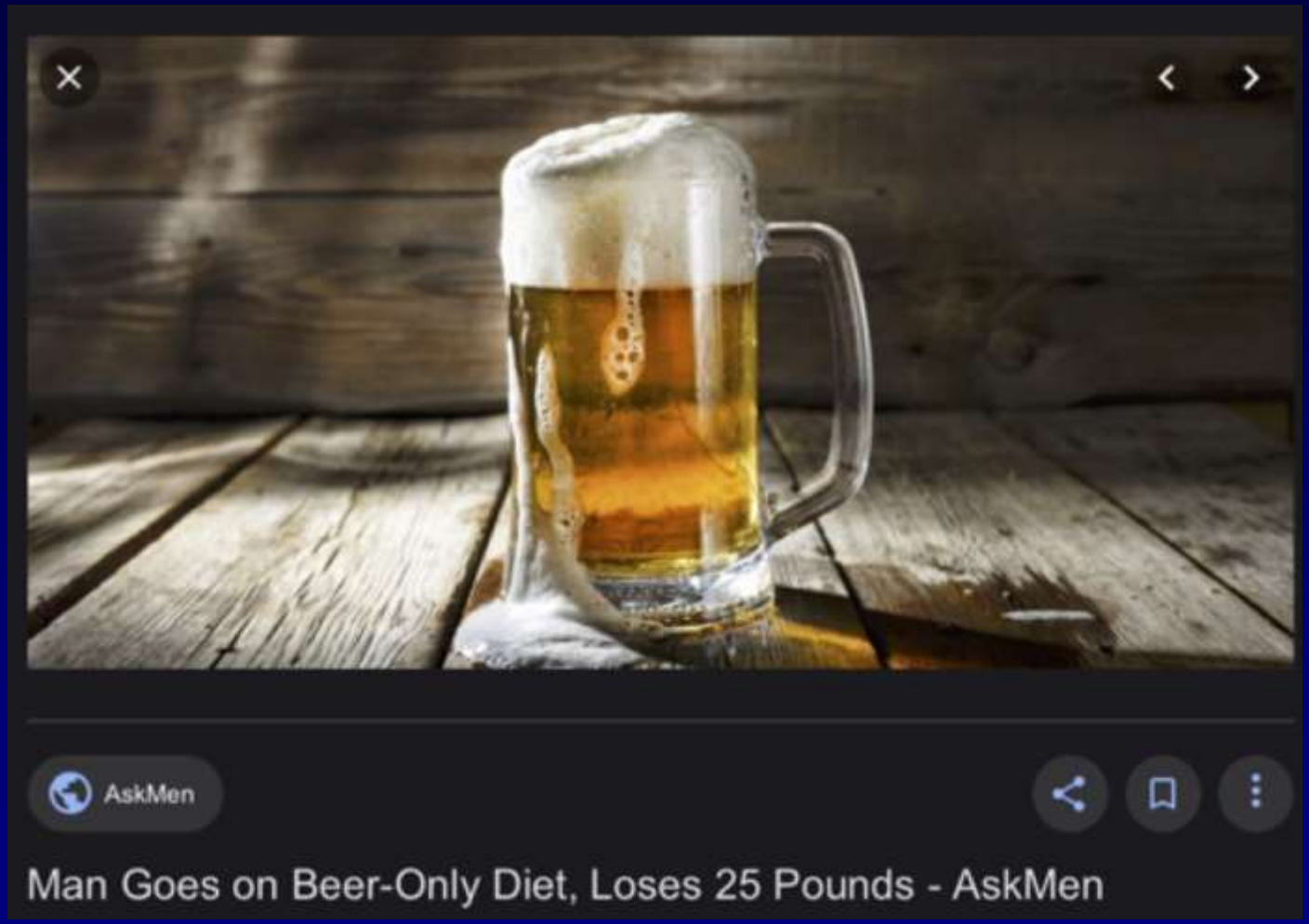
Colchicine - Side Effects

- GI effects
  - Purgative effect
- Narrow therapeutic window
  - Neuropathy, myopathy, bone marrow suppression
- Dose adjust for creatinine clearance
- IV colchicine
  - Tissue necrosis, acute renal failure, bone marrow aplasia
  - Don’t use it

Treatment Considerations

- Hyperuricemia is usually asymptomatic
  - Prevalence 5-8 %; 20% develop gout
- Onset in males age 30
  females postmenopausal
- Duration 10-15 yrs before clinical disease
- 90% due to undersecretion
  10% due to overproduction
- 50-60% incidence of recurrence after first attack within one year ; 80% within 2 yrs
- 2-7% will not have another attack after 10 yrs

Causes of Hyperuricemia



AskMen.com

Causes of Hyperuricemia

Overproduction

- Increased purine biosynthesis
  - Increased nucleic acid turnover
    - Myeloproliferative diseases
    - Hemolytic anemias
    - Psoriasis
  - Inherited enzyme defects
- Increased breakdown of ATP
    - Severe illness
    - Strenuous exercise
    - Excessive ethanol consumption
    - Glycogen storage disease

Causes of Hyperuricemia

Underexcretion

- Intrinsic renal disease
  - Renal insufficiency
  - Gout
  - Lead nephropathy
  - Endocrinopathy (hypothyroidism, hyper and hypoparathyroidism)
- Competition for excretion by organic acids
  - Drugs (e.g. thiazides, nicotinic acid, low-dose salicylates)
  - Lactic acid (e.g. lactic acidosis, heavy ethanol use)
  - Ketosis
  - Glycogen storage disease

Allopurinol

- Xanthine oxidase inhibitor
- Highly effective in lowering serum uric acid
  - annual gout attacks reduced from
    4.4 to .06 / yr
- Starting dose 300 mg/day
- Lifelong treatment
- Renally cleared - Must be dose adjusted

Allopurinol

- Rare but significant toxicity
  - Allopurinol hypersensitivity
  - Rash → Steven-Johnson Syndrome
  - rare but often fatal
  - Oxypurinol is an option but 50% intolerance
  - Febuxostat offers viable alternative
  - Risk directly related to serum level of drug Increased risk with CRI
- Hepatic and marrow toxicity. Not Renal
- Multiple interactions
  - azathioprine, 6MP, warfarin, theophylline, ampiciliin, diuretics

Febuxostat

- Febuxostat “Uloric”
  - Xanthine oxidase inhibitor
  - 40-80 mg po qd
  - No dose reduction for renal, hepatic insufficiency
  - Prophylaxis for acute gout required
  - Most common AEs are LFT elevation, nausea, rash arthralgias
  - Contraindicated with azathioprine, 6-MP, theophyline
- Effectively lowers serum uric acid
- Effective and safe in patients with history of allopurinol sensitivity
- Inreased CV risk? Black Box Warning

Efficacy of febuxostat vs allopurinol

Outcome	Febuxostat 80 mg (%)	Febuxostat 120 mg (%)	Allopurinol 300 mg (%)	p
Serum urate <6.0 mg/dL	53	62	21	<0.001 febuxostat 80 mg and 120 mg vs allopurinol
Incidence of gout flares at weeks 9-52	64	70	64	0.99 for febuxostat 80 mg vs allopurinol 0.23 for febuxostat 120 mg vs allopurinol
Median reduction in tophus area	83	66	50	0.08 for febuxostat 80 mg vs allopurinol 0.16 for febuxostat 120 mg vs allopurinol

Michael A. Becker, M.D., H. Ralph Schumacher, Jr., M.D., Robert L. Wortmann, M.D., et al., “Febuxostat Compared with Allopurinol in Patients with Hyperuricemia and Gout,” *NEJM*, 354:1352, 2006.

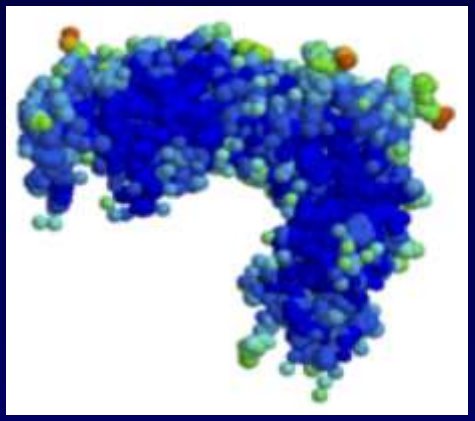
ULT (Allopurinol)

- Effective in preventing acute gout
- Absolutely indicated for tophaceous gout and chronic gout
- Gradual reduction in size of tophi if uric acid < 6 mg/dl
- Titrate dose gradually upward to bring uric acid into low normal range
- Dose adjust for renal function but not contraindicated with CKD

Uricosurics

- probenecid
  - 500 mg tabs
  - bid dosing
  - 1-3 grams / day
- Vitamin C

New Treatments



- Uricase
  - Converts uric acid to allantoin
  - Rasburicase
    recombinant uric acid oxidase
    "Elitek"
  - parenteral route – can be given only once due to antibody production
  - Black box warning – anaphylaxis, hemolysis, methemoglobinemia
  - Pegylated preparation Pegloticase, Krystexxa

- URAT 1 Inhibitors
  - Lesinurad

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

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

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

C

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

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

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

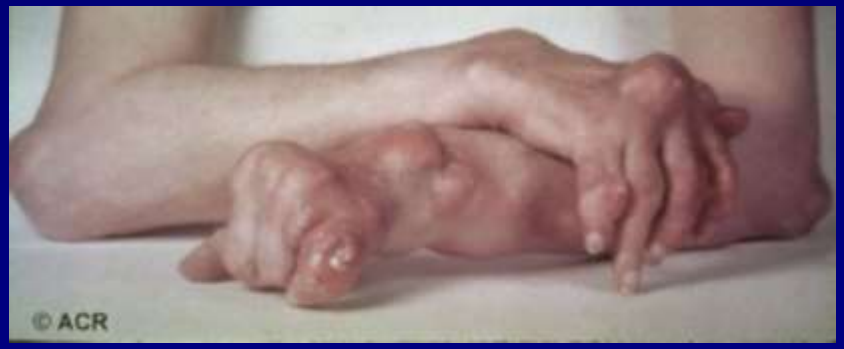
2012 ACR Guidelines for Management of Gout. Arthritis Care & Research, Vol. 64, No. 10, October 2012, pp 1431–1446

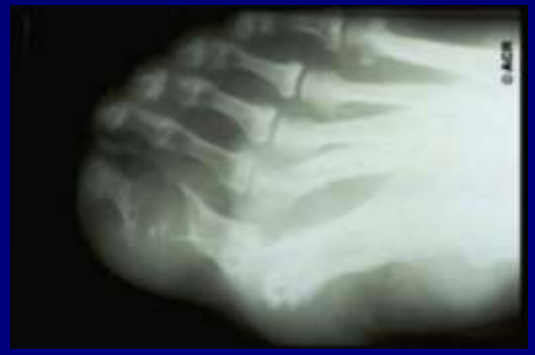
Baseline Treatment Considerations

- Patient Education (diet/lifestyle)
- Consider secondary causes
- Consider elimination of non-essential medications
- Consider disease burden of gout

Chronic Gout

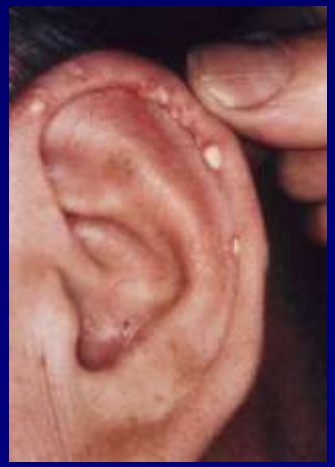
- Generally develops after >10 years of intercurrent gout
- Characterized by tophi deposition
  - joints, tendons, soft tissues
- Chronically swollen ands inflamed joints
- Joint destruction
- Usually requires chronic anti-inflammatory therapy in addition to allopurinol

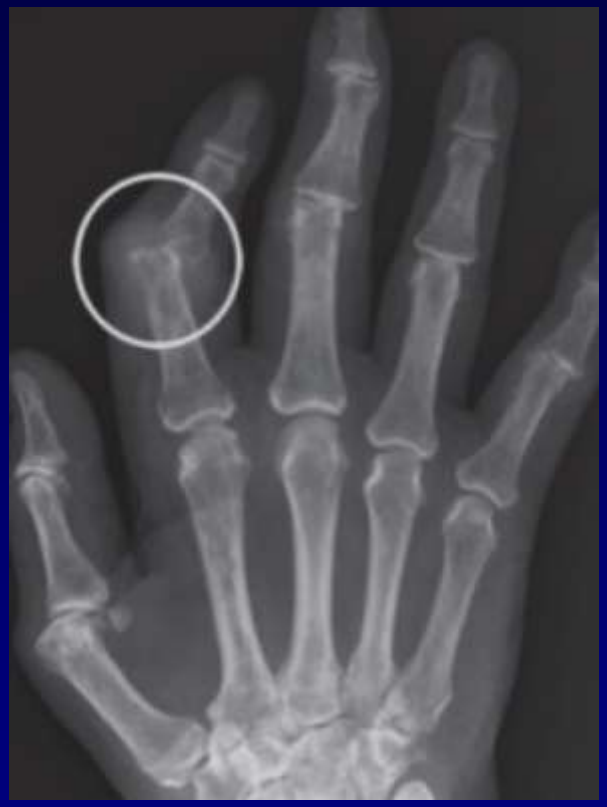


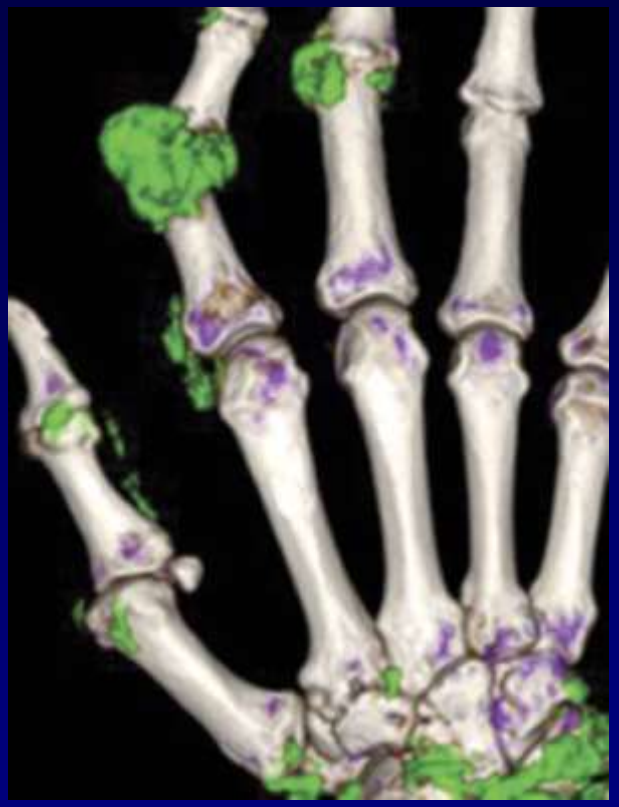


Tophaceous Gout

Deposition of crystalline monosodium urate







Gout and CV Risk

- Hyperuricemia and clinical gout are strongly linked to HTN, CV disease, metabolic syndrome and CKD
- Hyperuricemia strongly associated elevated hs-CRP
- Cause vs association

Swedish CArdioPulmonary bioImage Study (SCAPIS)

Urate quartiles, µmol/L	Men (*N*=508)				Urate quartiles, µmol/L	Women (*N*=532)			
	OR, univariable	*p* value	OR, multivariable	*p* value		OR, univariable	*p* value	OR, multivariable	*p* value
	CAC examined (*N*=508)[a] CAC+ (*N*=293)					CAC examined (*N*=532)[a] CAC+ (*N*=137)			
31–307, ref	1		1		143–229, ref	1		1	
308–346	1.6 (1.0–2.7)	0.049	2.2 (1.2–4.0)	0.008	230–262	1.0 (0.6–1.8)	0.97	0.8 (0.4–1.6)	0.5
347–391	1.6 (0.9–2.5)	0.08	1.9 (1.0–3.6)	0.04	263–304	1.1 (0.6–1.9)	0.8	1.0 (0.5–1.9)	0.9
392–584	2.0 (1.2–3.4)	0.007	2.3 (1.2–4.4)	0.01	305–702	1.5 (0.9–2.6)	0.2	1.0 (0.5–2.0)	0.96
	CIMT examined (*N*=436)[a] CIMT+ (*N*=106)					CIMT examined (*N*=475)[a] CIMT+ (*N*=117)			
31–307, ref	1		1		143–229, ref	1		1	
308–346	1.5 (0.8–2.7)	0.2	1.2 (0.6–2.4)	0.5	230–262	1.2 (0.6–2.2)	0.6	1.2 (0.6–2.3)	0.7
347–391	0.9 (0.5–1.7)	0.7	0.7 (0.3–1.4)	0.3	263–304	1.3 (0.7–2.4)	0.4	1.0 (0.5–2.1)	0.9
392–584	1.3 (0.7–2.5)	0.4	0.9 (0.4–1.8)	0.7	305–702	1.6 (0.9–2.9)	0.1	1.0 (0.5–2.2)	0.99
	Carotid plaque examined (*N*=507)[a] Plaque+ (*N*=308)					Carotid plaque examined (*N*=526)[a] Plaque+ (*N*=268)			
31–307, ref	1		1		143–229, ref	1		1	
308–346	1.6 (0.95–2.6)	0.08	1.8 (1.0–3.2)	0.03	230–262	0.8 (0.5–1.3)	0.4	0.9 (0.5–1.6)	0.7
347–391	1.2 (0.7–1.9)	0.6	1.1 (0.6–2.0)	0.7	263–304	1.1 (0.7–1.7)	0.8	1.3 (0.7–2.2)	0.4
392–584	1.5 (0.9–2.4)	0.1	1.6 (0.9–2.9)	0.2	305–702	0,99 (0.6–1.6)	0.95	1.1 (0.6–2.1)	0.7

Drivelefka,P, et al., Arthritis Res and Therapy, 22:37 , 2020

Gout and CV Risk

Potential benefit ot uric acid?

- Serum urate has potent antioxidant activity
- Uric acid improves endothelial and mitochondrial function

ULT and CV Risk

CARES noninferiority safety trial of febuxstat vs allopurinol

- No difference in composite CV endpoint
- Increased CV events and all-cause mortality on febuxostat group
- Trend towards increased mortality in gout patients randomized to more intensive urate-lowering therapy

White EB, et at., N Engl J Med. 2018;378:1200–1210

Uric Acid – too little of a bad thing?

- U-shaped association of serum urate levels with mortality in some observational studies.
- Association of lower serum urate with worse neurological outcomes
- Question of increased CV risk at low uric acid levels

Uric Acid and CV Risk

- Prospective outcome studies or ULT are lacking
- relationship to cardiovascular disease, CKD and diabetes remains controversial

2016 ACP Treatment Guidelines

- Treat acute gout with corticosteroids, NSAIDs, or colchicine
- Use low-dose colchicine in treating acute gout
- Do not to begin ULT after a first gout attack or in patients with 2 or fewer/yr
- Discuss benefits, harms, costs, and individual preferences before initiating ULT in patients with recurrent attacks *

* Evidence is insufficient for monitoring of serum urate Levels

2012 ACR Treatment Guidelines

- Baseline Recommendations for gout care
  - patient education
  - consider secondary causes
  - consider d/c of nonessential medications
  - evaluate disease burden (tophi)
- Indications for urate lowering therapy
  - tophaceous disease
  - frequent attacks of acute gout (≥2/yr)
  - CKD (Stage 2 or worse)
  - h/o urolithiasis
- Treat to serum uric acid target
  - < 6 mg/dL; < 5 mg/dL may be needed

Why the Difference?

- Methods for guideline development
  - Strength of evidence

    A: Supported by multiple randomized clinical trials or meta-analyses

    B: Derived from a single randomized trial or nonrandomized studies

    C: Consensus opinion of experts, case studies, or standard of care
- Conflict of Interest?
- Clinical Orientation

2019 ACR Treatment Guidelines

- Indications for urate lowering therapy (ULT)
  - Tophaceous disease
  - Radiographic damage
  - Frequent attacks of acute gout (≥2/yr)
  - [After 1st flare if CKD3, SUA >9, urolithiasis]
- Initial ULT
  - Allopurinol
  - HLA B*5801 testing in SE asian and AA patients
  - Initiate XOI or UU at low dose
  - Concomitant anti-inflammatory therapy
  - ULT during flare OK
- Treat to serum uric acid target < 6 mg/dL

Uncontrolled Gout – An Ongoing Problem

- Low initiation of ULT
- Underutilization of ULT
- Poor treatment compliance
- Unanswered questions

  [Cause or effect]

  – Renal disease

  – Metabolic syndrome

  – CV risk