Gout:

Updates on Immunopathology and Treatment Implications

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Disclosures

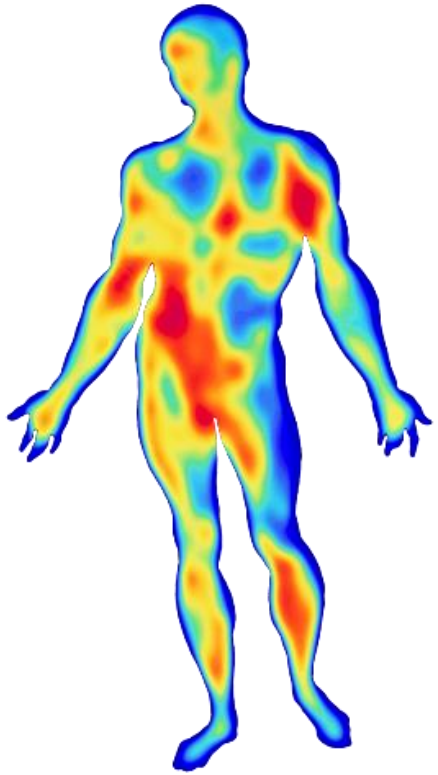
1. Horizon Pharma, Plc: Research; Consultant; Speaker Bureau

Objectives

- To review gout as a chronic, progressive arthropathy
- To discuss the latest concepts of the immunopathology of gout
  - Gout is an autoinflammatory disease
  - Gout is associated with perturbations in innate immunity: NLRP3 inflammasome and neutrophil extracellular traps (NETs)
- To consider treatments implications based on our evolving understanding of the etiopathogenesis of gout
- To review the 2020 updates to the ACR Gout Treatment Guidelines
- To change the treatment paradigm of gout in clinical practice

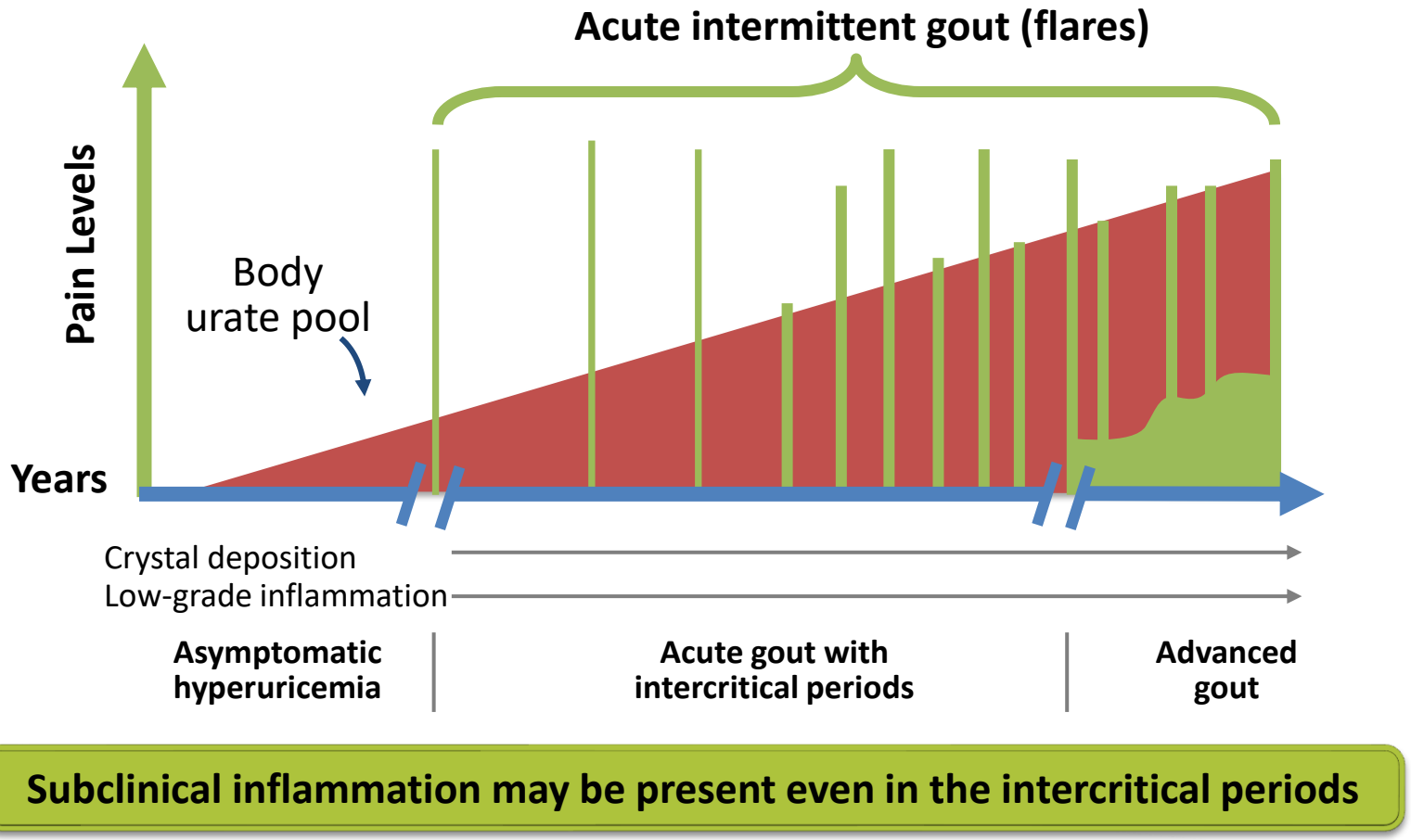
Gout definition

- An inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals in synovial fluid and other tissues
  - Crystal deposition occurs when serum uric acid (SUA) concentration exceeds its solubility
  - As gout progresses, crystal deposition can occur anywhere in the body
  - Chronic disease can lead to sequelae including:
    - Bone erosions
    - Tophi
    - Chronic pain
    - Joint deformities
    - Loss of function
    - Disability



Temperature	Calculated Urate Solubility (mg/dL)*
37°C (98.6°F)	6.8
35°C (95.0°F)	6.0
30°C (86.0°F)	4.5

Gout is a chronic, progressive disease

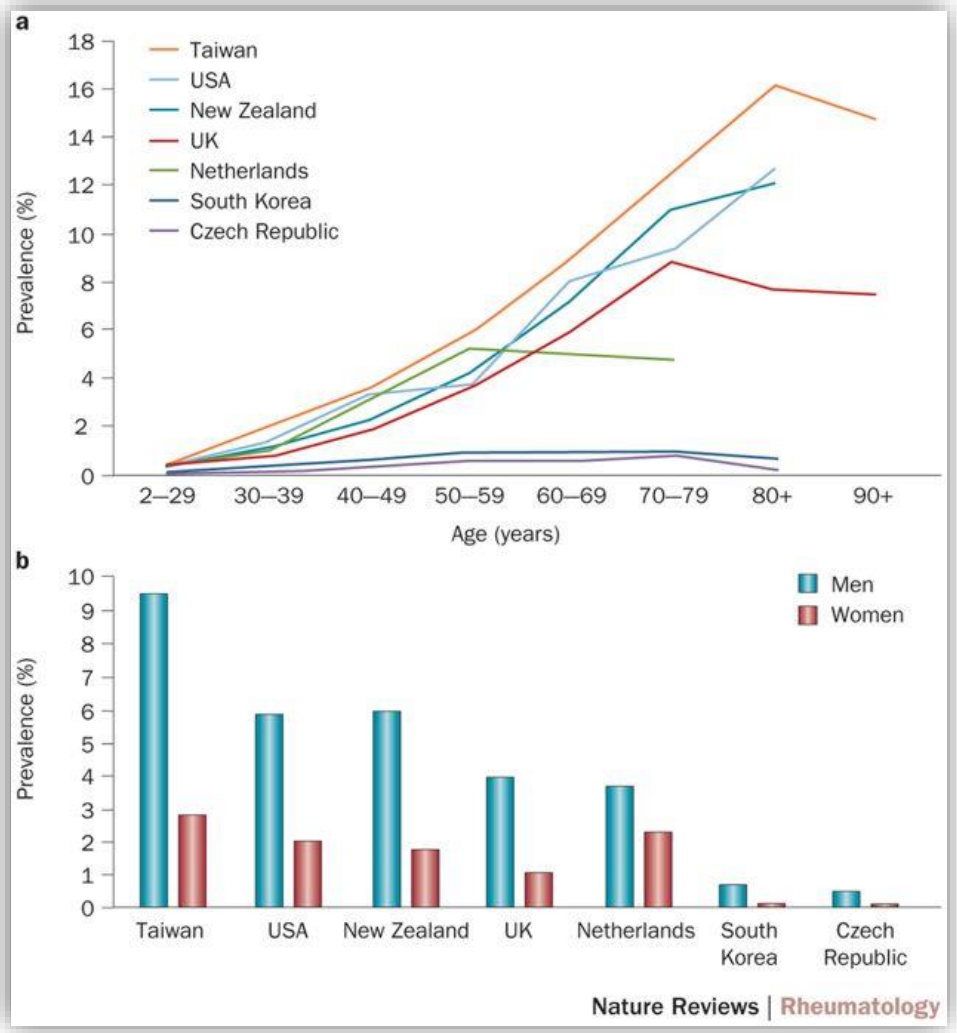


Subclinical inflammation may be present even in the intercritical periods

Adapted from Edwards NL. Gout. A. Clinical features. In: Klippel JH, Stone JH, Crofford LJ, White PH, eds. *Primer on the Rheumatic Diseases*. 13th ed. New York: Springer; 2008:241-249.

Prevalence

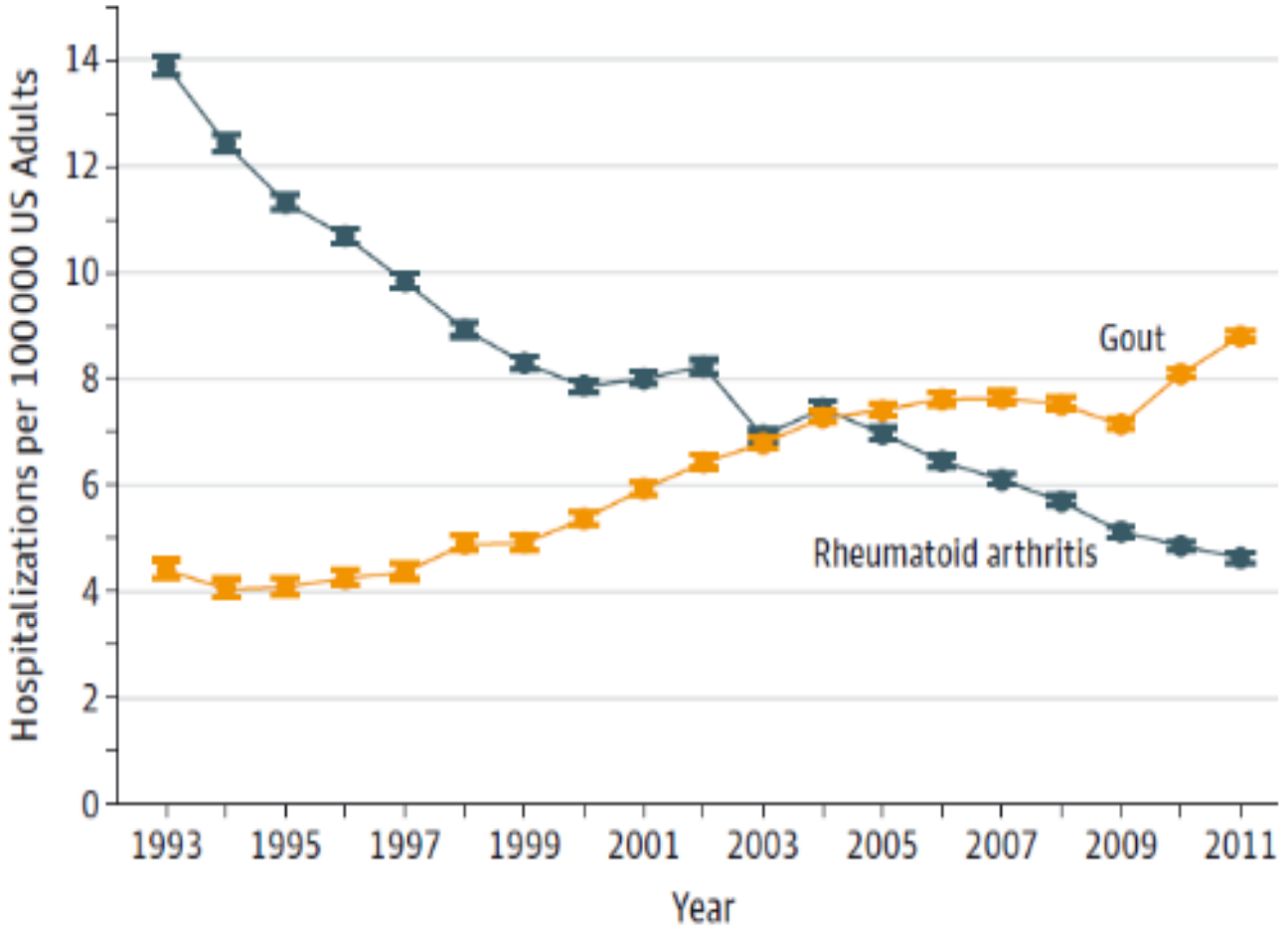
- Gout is the most common form of inflammatory arthritis
- Incidence is greater in men than in women
- Incidence increases with age
  - Mainly due to proportional decline in renal function
- Est. prevalence in U.S. 2019: 3.9% (9.2 million) Chen-Xu M et al. *Arthritis Rheumatol*. 2019;71:991-999
- Prevalence is increasing worldwide



Kuo C-F, et al. *Nature Reviews Rheumatology*. 2015;11:649-662

Hospitalization Rates 1993 - 2011: RA versus Gout

- Annual hospitalization rate per 100,000 adults for RA declined from 13.9 to 4.6
- During the same period, hospitalization rate for gout increased from 4.4 to 8.8
- Hospital admission costs for gout in 2005: $11.2 billion (up from $0.76 billion in 1998)

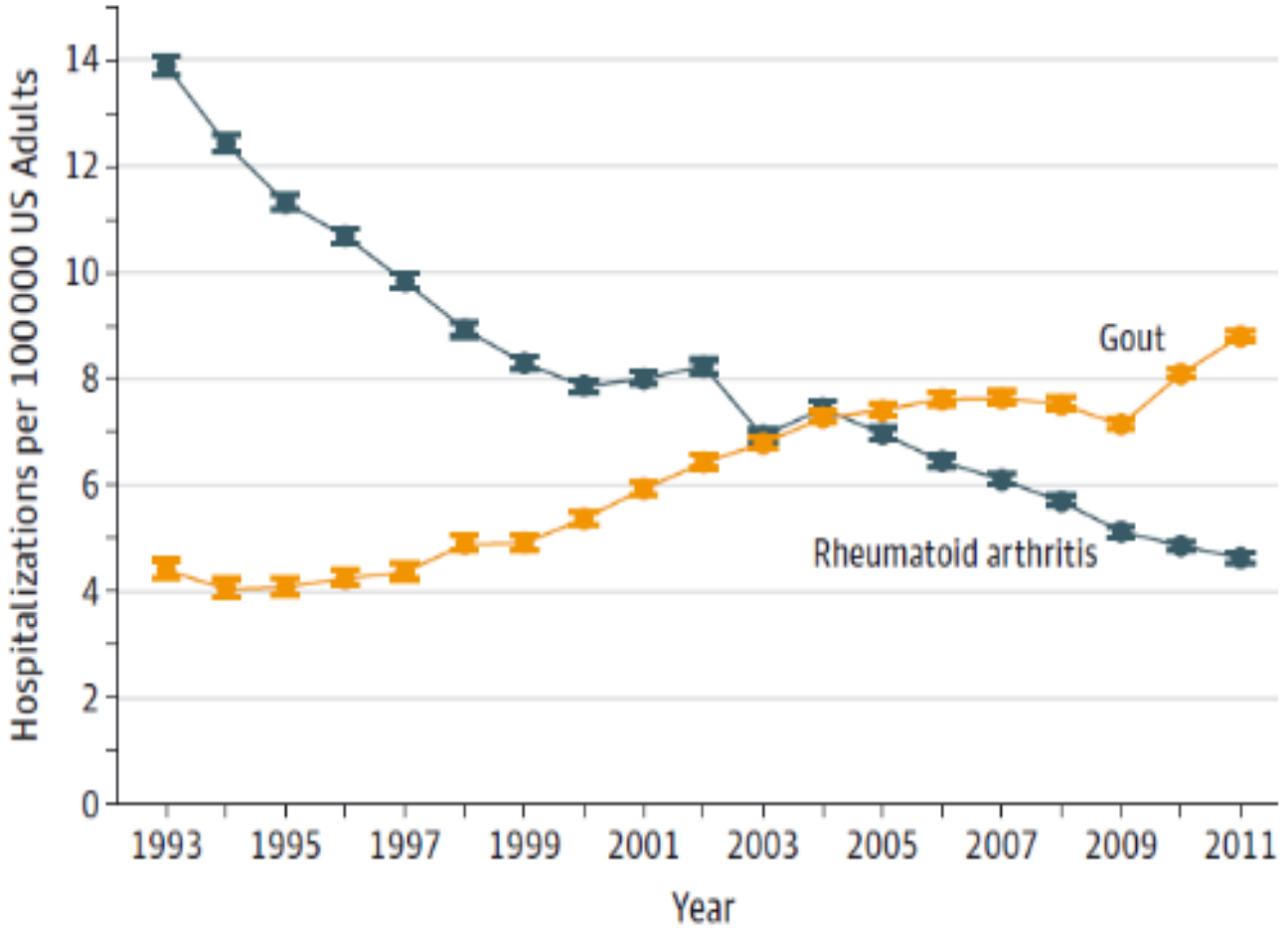


Schlesinger 2011; Lim 2016

Hospitalization Rates 1993 - 2011: RA versus Gout

Reasons for RA improvement:

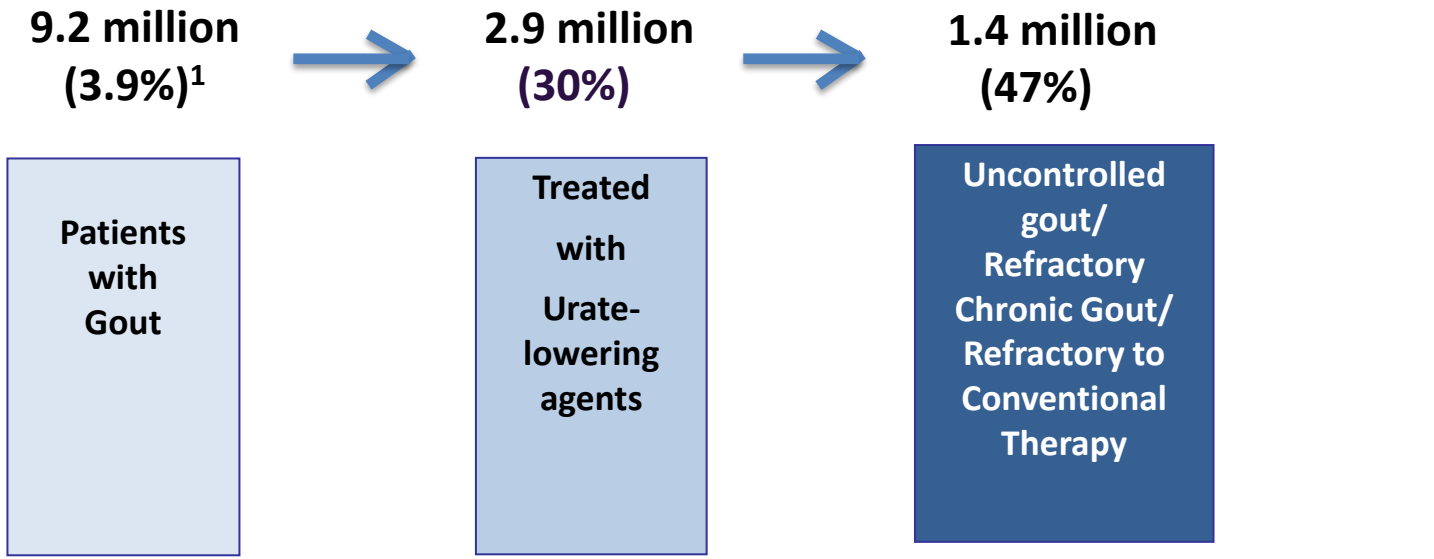
- Better understanding of etiopathogenesis of disease
- Emphasis on early detection and diagnosis
- Adoption of aggressive treatment strategies
- Embrace of treat-to-target approach
- Robust therapeutic development
- Goal of remission/functional cure

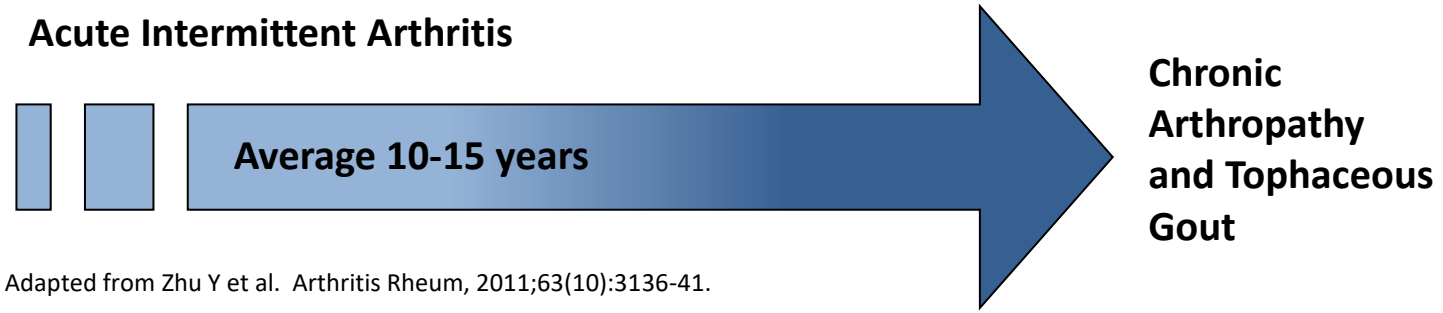


Schlesinger 2011; Lim 2016

Spectrum of Gout

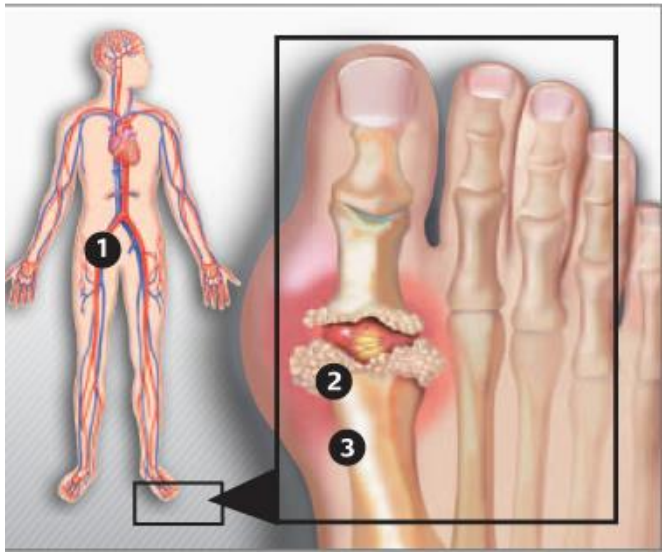
Estimated number of affected persons in the US

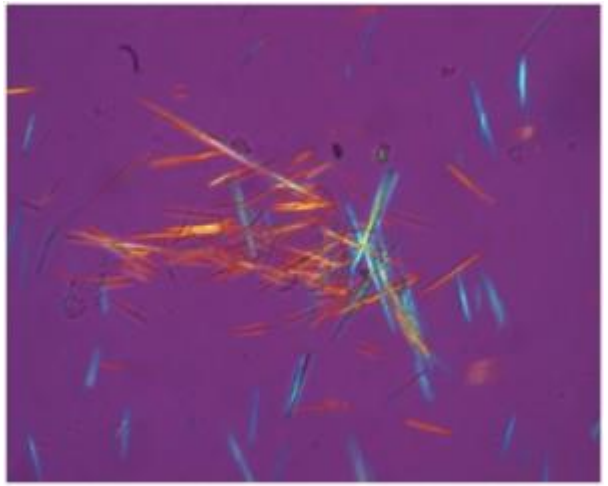


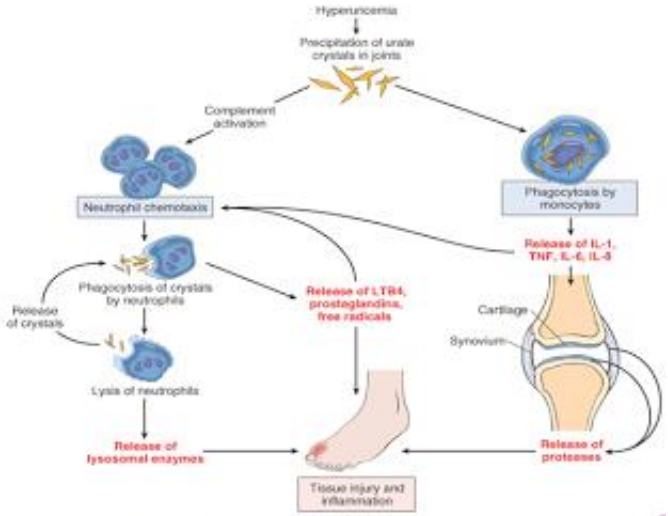


Adapted from Zhu Y et al. Arthritis Rheum, 2011;63(10):3136-41.

Etiopathogenesis of Gout





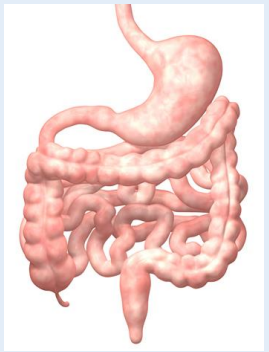


Pathogenesis of acute gouty arthritis

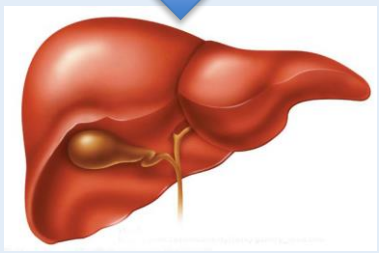
Regulation of uric acid

Normal Human Uric Acid Turnover

- Dietary intake

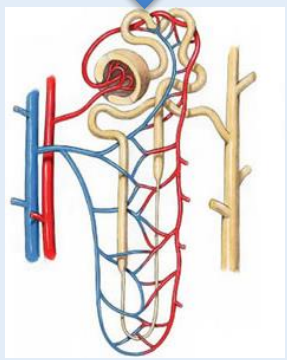


- Normal cellular degradation
- De novo purine synthesis
- Psoriasis
- Malignancy
- Tumor lysis syndrome



- Muscular exercise

- Purine catabolism in other organs (lungs, brain, etc.)



Excretion GI tract (25-33%)

Excretion Kidney (66-75%)

Causes of hyperuricemia

Under-excreters of urate (~90%)

Clinical Disorders

- Chronic renal failure
- Lead nephropathy
- Polycystic kidney disease
- Familial juvenile hyperuricemic nephropathy
- Medullary cystic kidney disease
- HTN
- Dehydration
- Salt restriction
- Starvation
- Diabetic ketoacidosis
- Lactic acidosis
- Obesity
- Hyperparathyroidism
- Hypothyroidism
- Diabetes insipidus
- Sarcoidosis
- Toxemia of pregnancy
- Bartter's syndrome
- Chronic beryllium disease
- Down syndrome

Drugs or Dietary Habits

- Diuretics
- Low doses of salicylates
- Ethambutol
- Pyrazinamide
- Laxative abuse (alkalosis)
- Levodopa
- Methoxyflurane
- Cyclosporine
- Tacrolimus

Overproducers of urate (~10%)

Inherited Enzyme Defects

- HPRT deficiency
- Increased PRPP synthetase
- Glucose 6- phosphatase deficiency (glycogenosis I)

Clinical Disorders Leading to Purine Overproduction

- Myeloproliferative disorders
- Lymphoproliferative disorders
- Polycythemia vera
- Malignant diseases
- Hemolytic disorders
- Psoriasis
- Obesity
- Tissue hypoxia
- Glycogenosis III, V, VII

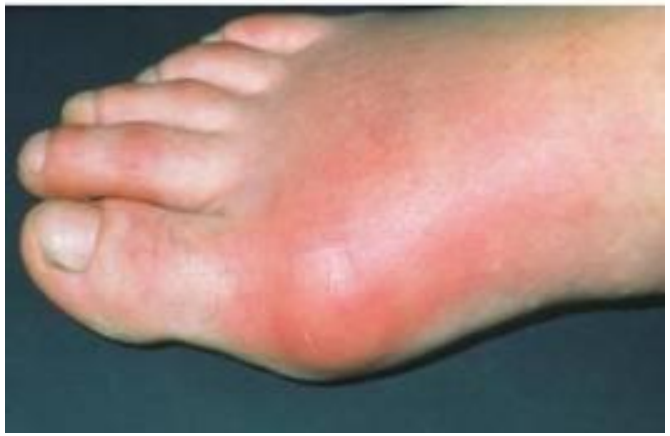
Drugs or Dietary Habits

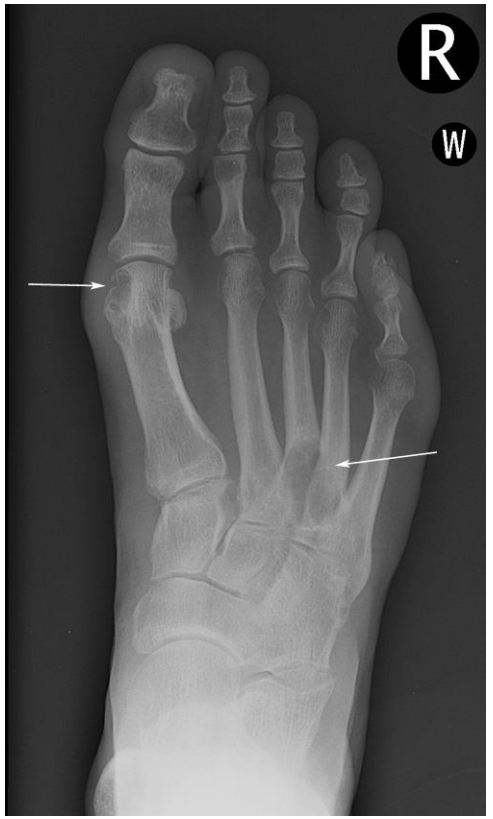
- Ethanol
- Diet rich in purines
- Pancreatic extract
- Fructose
- Nicotinic acid
- Ethylamino-1,3,4-thiadiazole
- 4-Amino-5-imidazole carboxamide riboside
- Vitamin B12 (patients with pernicious anemia)
- Cytotoxic drugs
- Warfarin

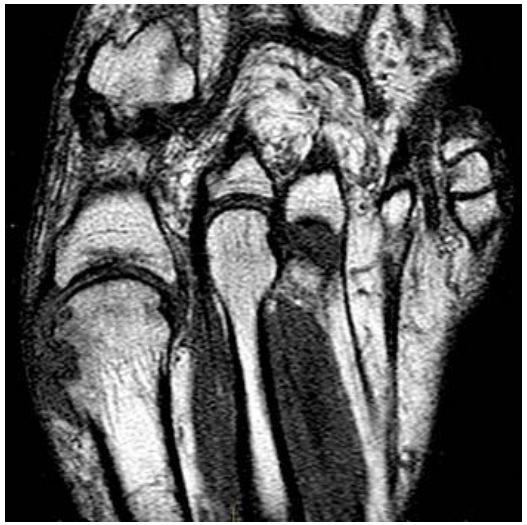
Becker MA, Jolly M. Clinical gout and the pathogenesis of hyperuricemia. In: Koopman WJ, Moreland, LW, eds. *Arthritis & Allied Conditions*. 15th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005:chap 113.

Urate deposition in the body

Joints

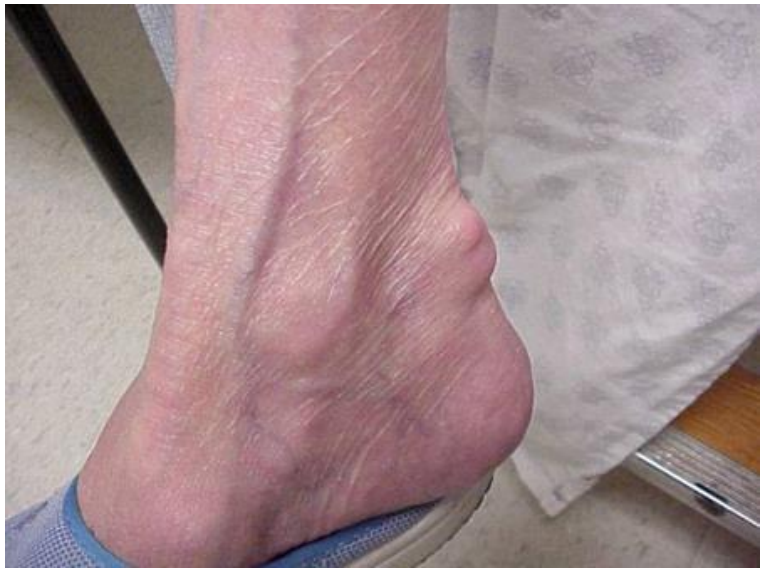


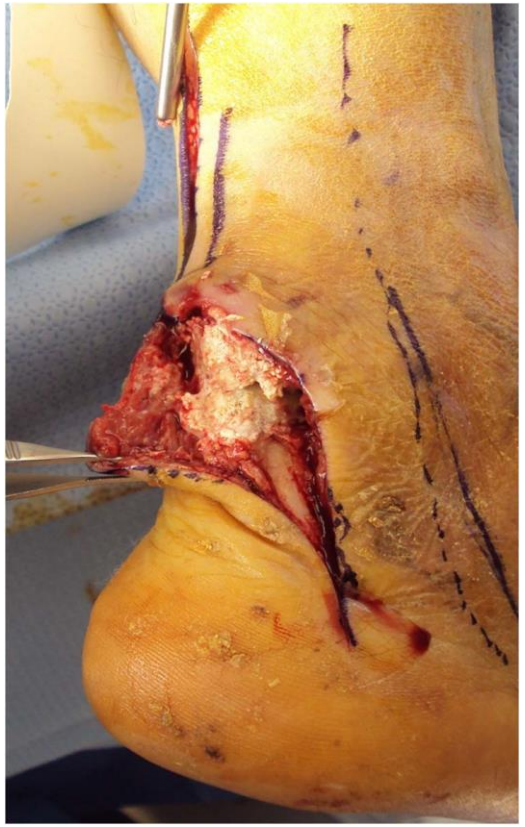




Urate deposition in the body

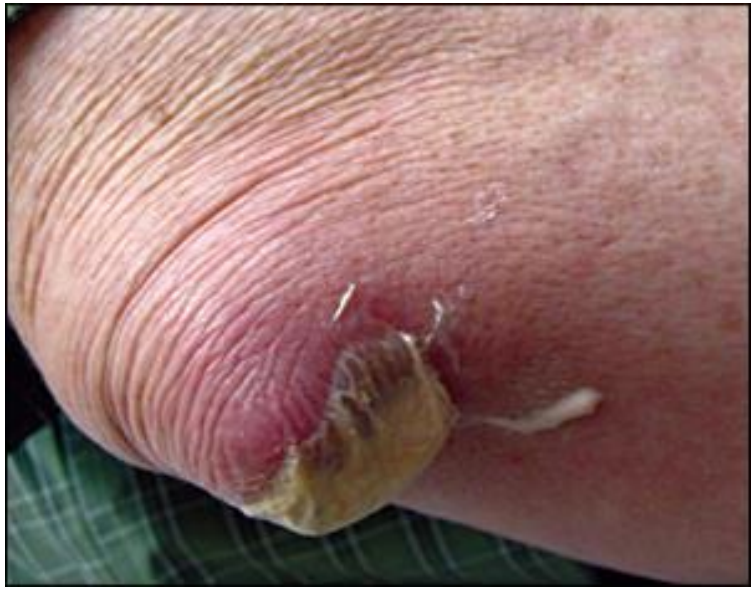
Tendons

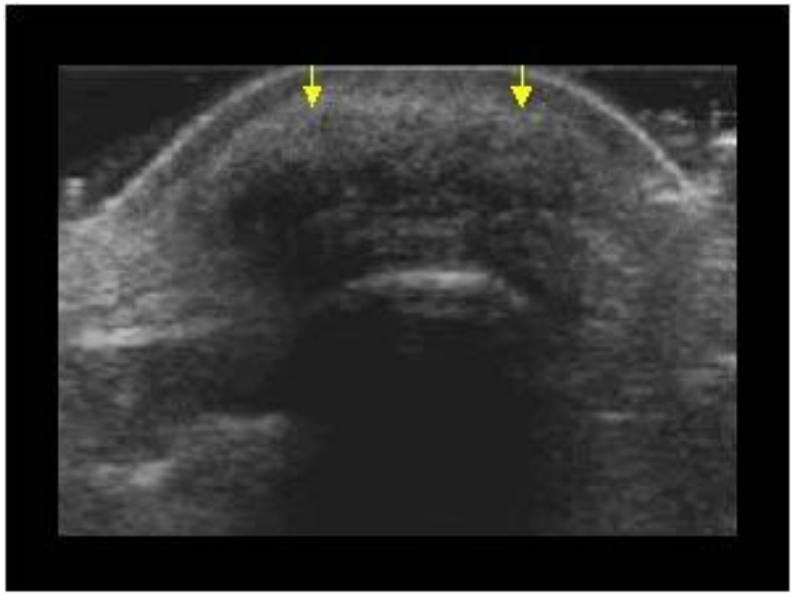




Urate deposition in the body

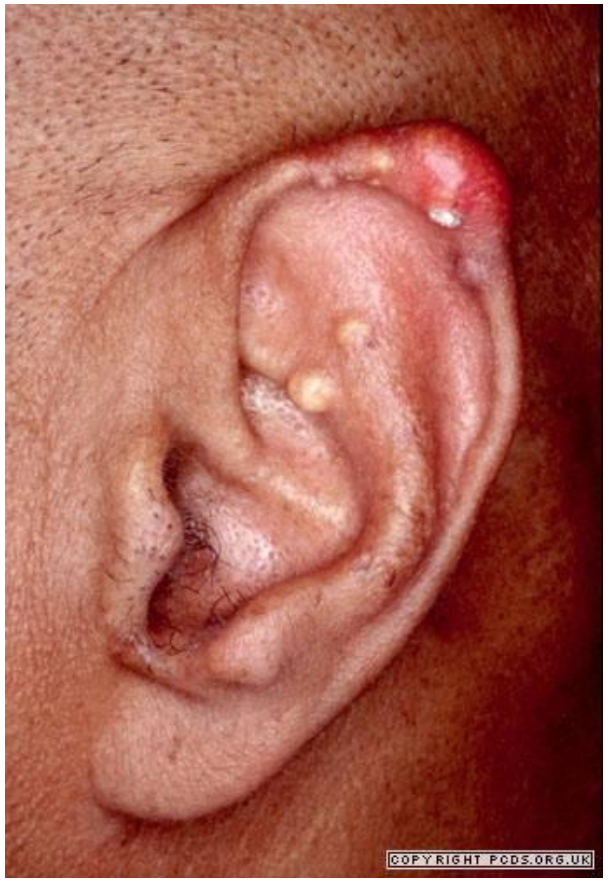
Bursae





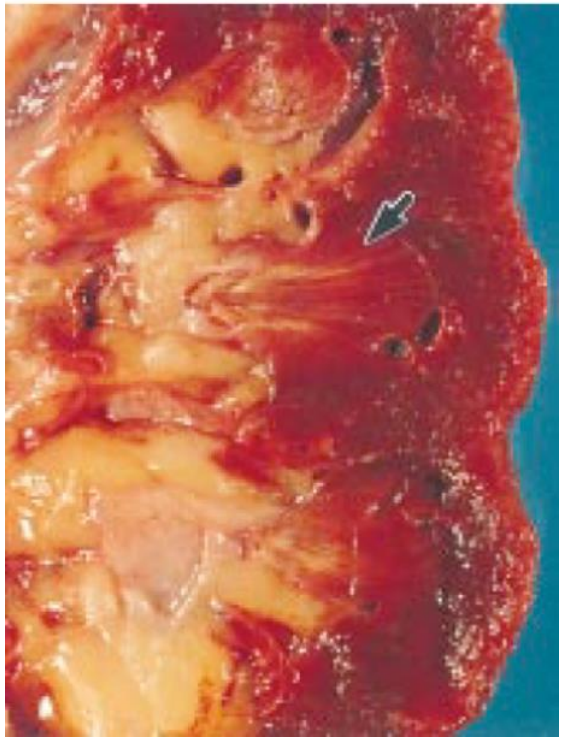
Urate deposition in the body

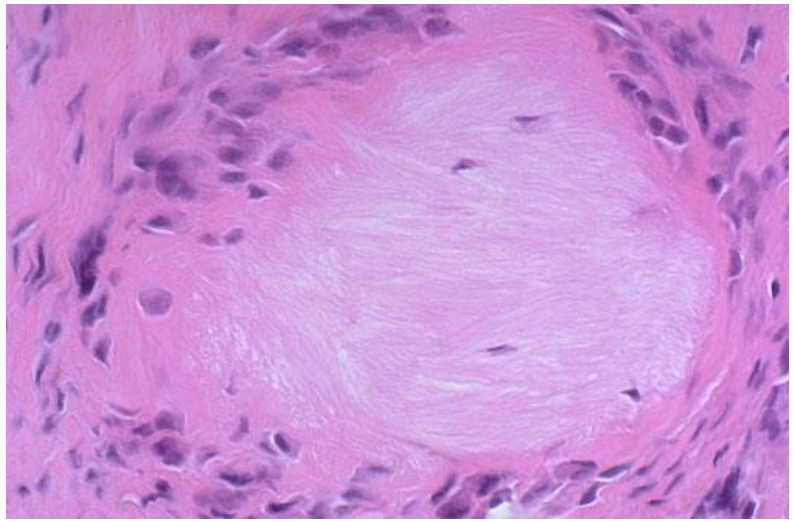
Ears



Urate deposition in the body

Kidneys

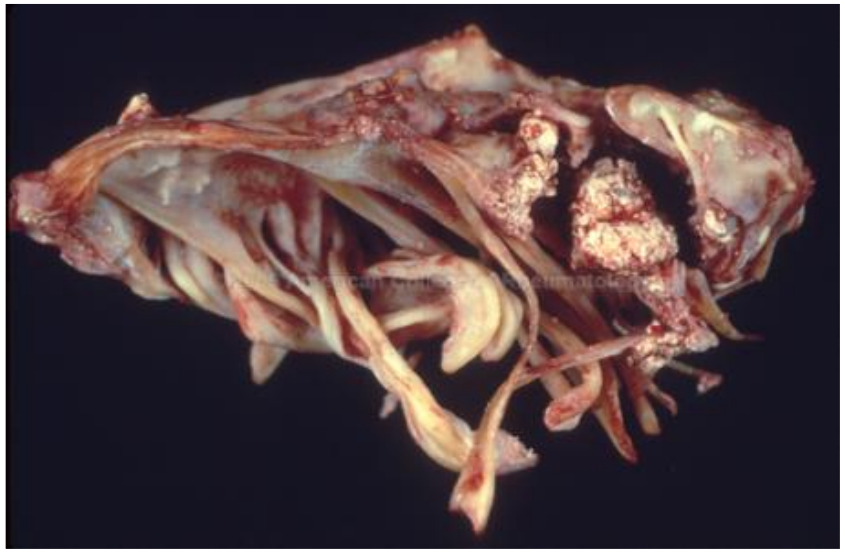




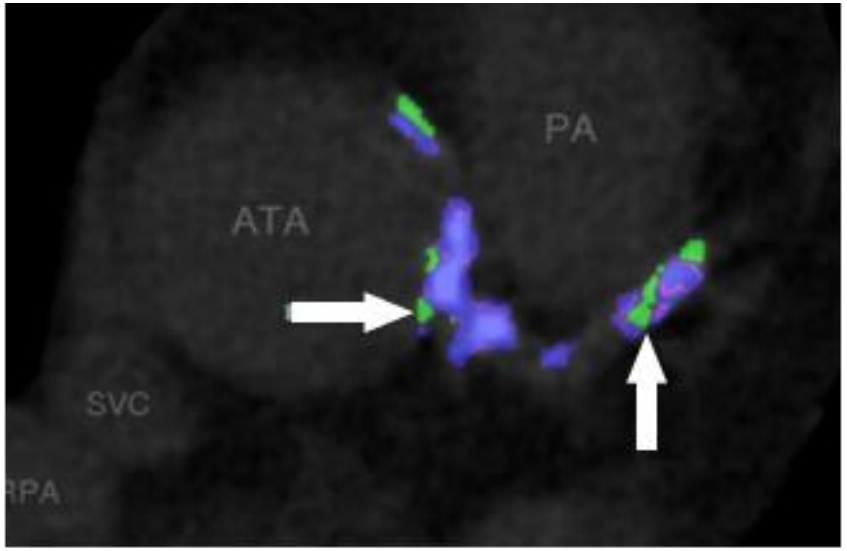
Urate deposition and fibrosis

Urate deposition in the body

Heart



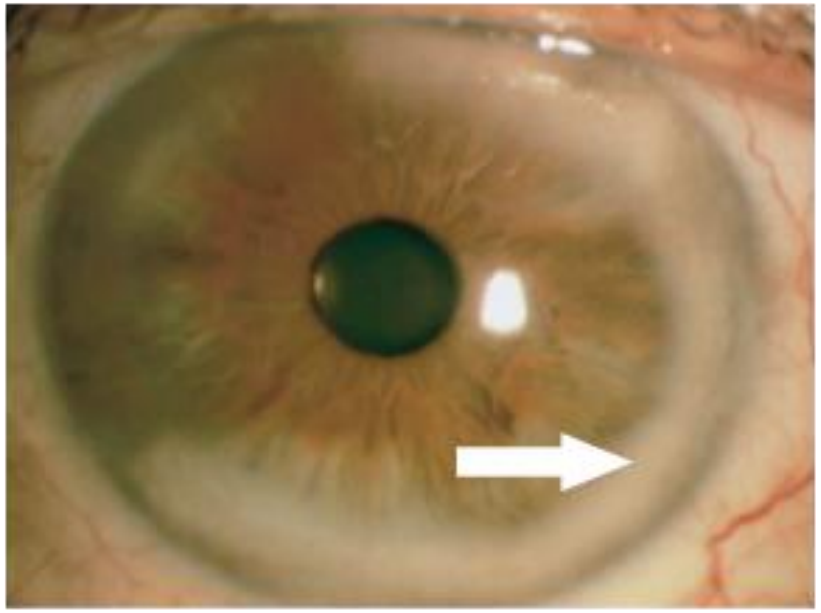
Pathology: Mitral Valve



DECT: Uric acid (in green) in thoracic aorta and coronary artery[10]

Urate deposition in the body

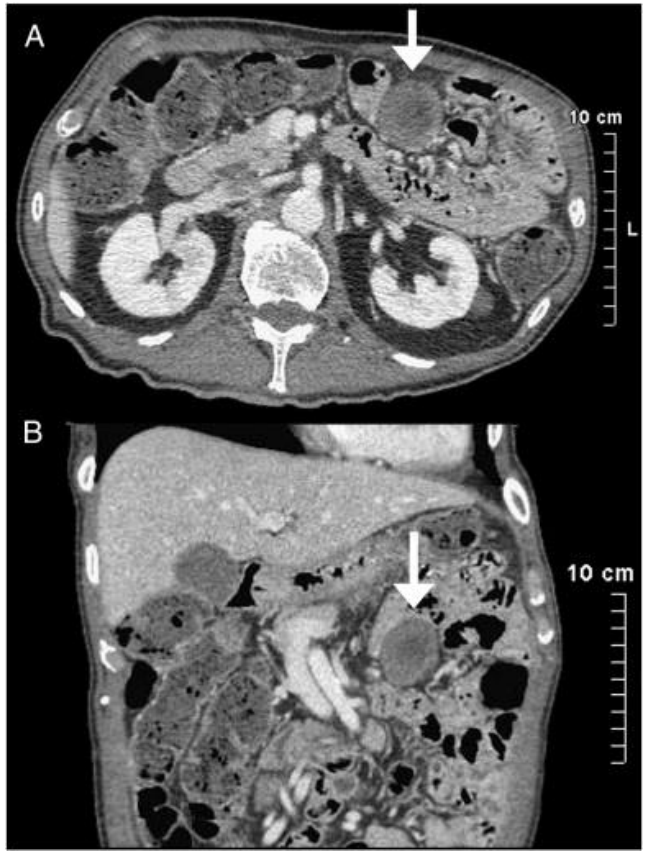
Eye

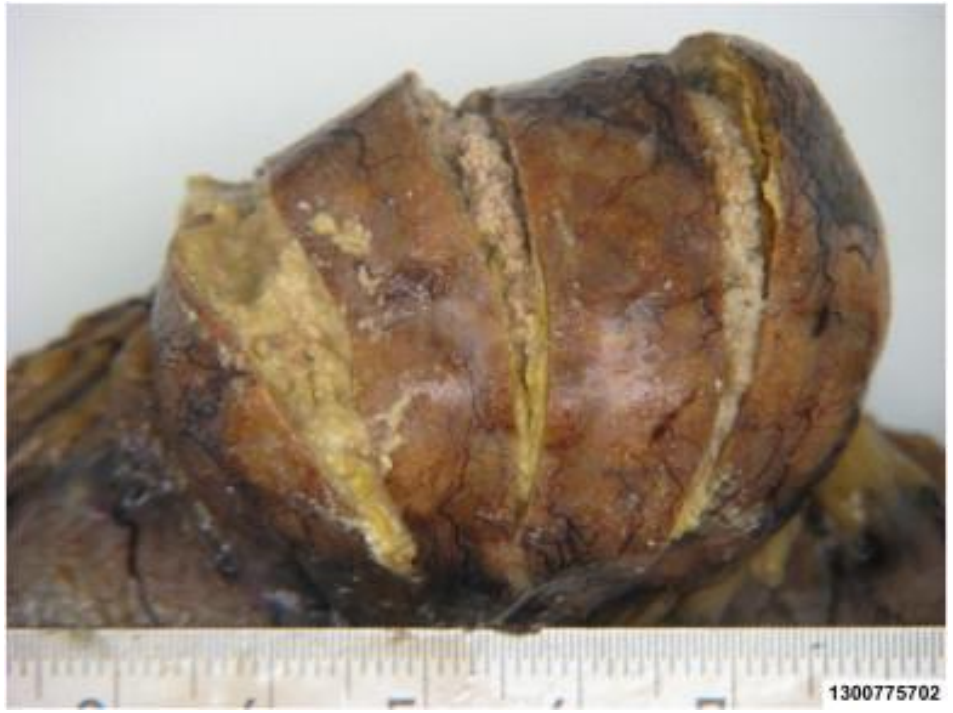


Photograph: Corneal tophus deposition in gout[1]

Urate deposition in the body

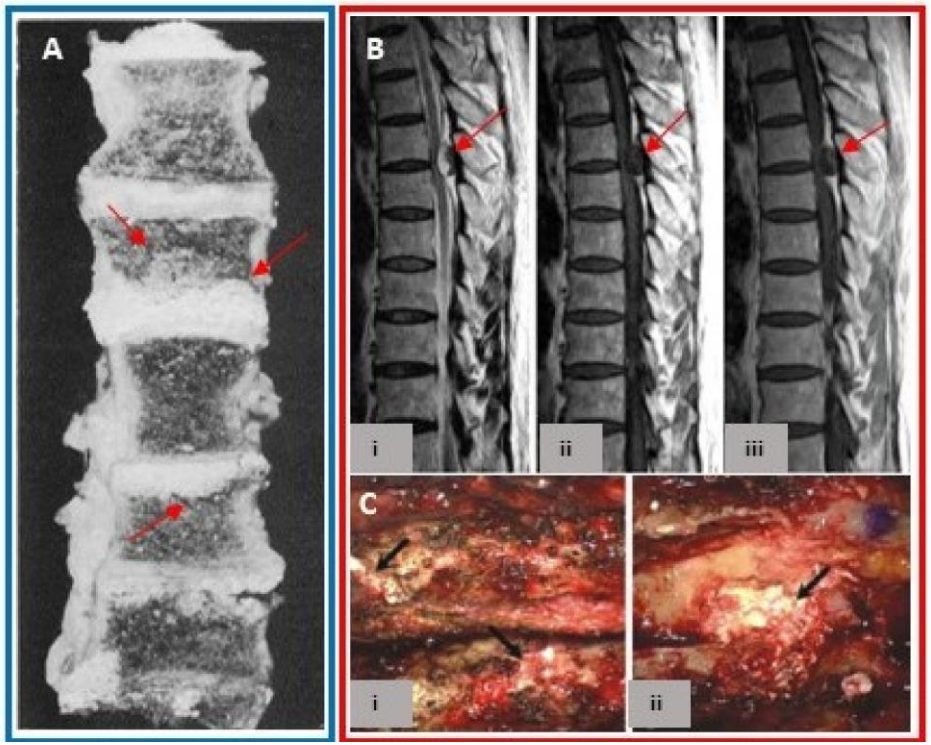
Small intestine
Mimicking a tumor

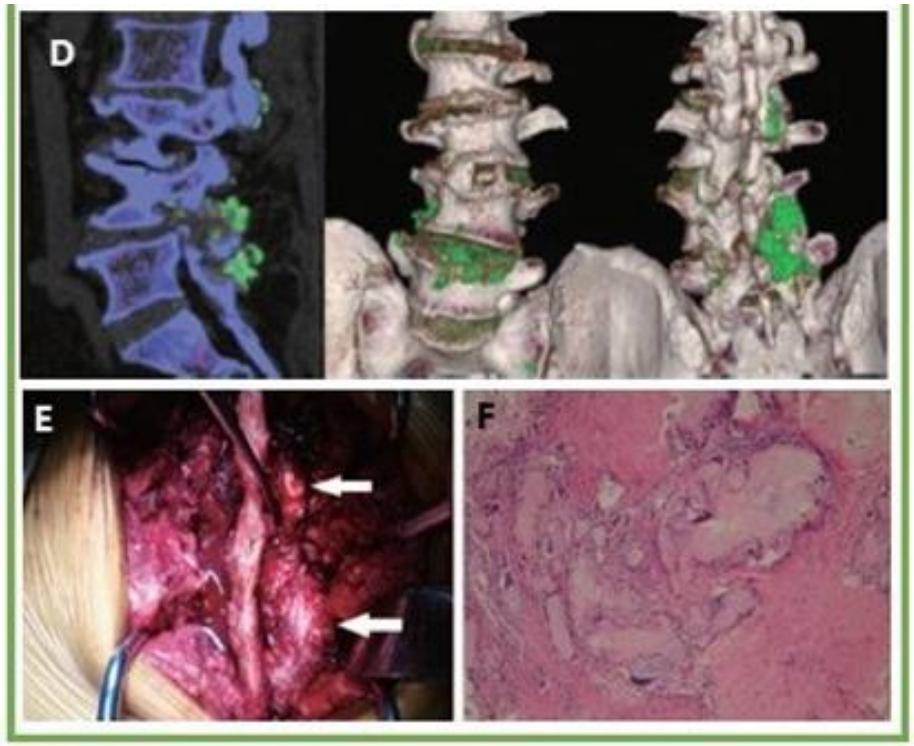




Urate deposition in the body

Spine

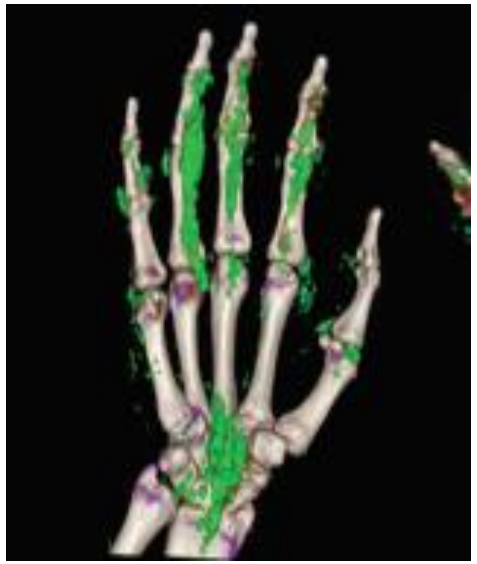




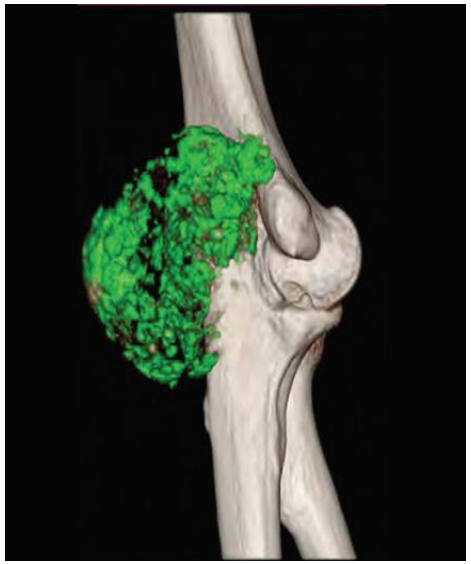
Khanna P, et al; J Clin Med 2020, 9(10):3204

Duel Energy CT (DECT) imaging of urate deposition

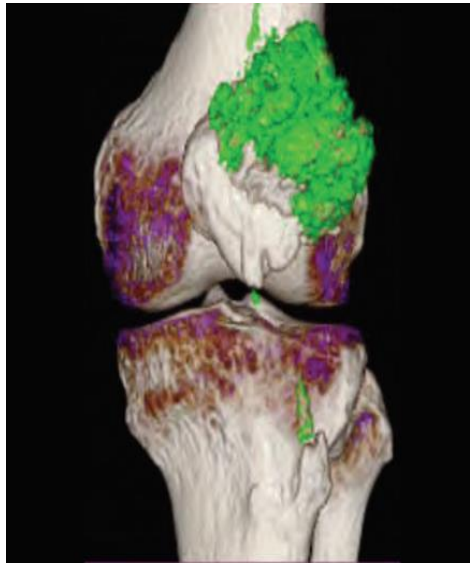
DECT imaging show that a majority of gout patients have non-visible tophi



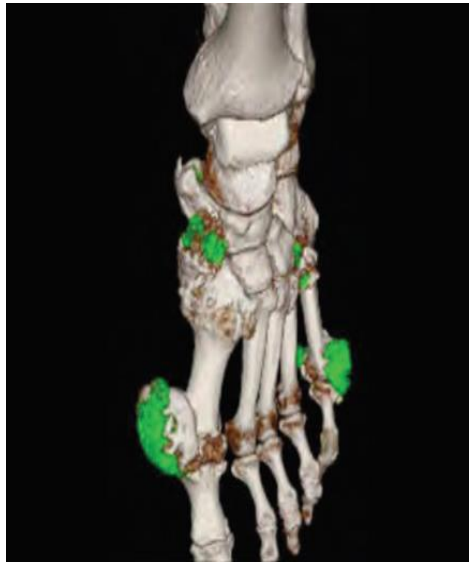
Hands



Elbows



Knees

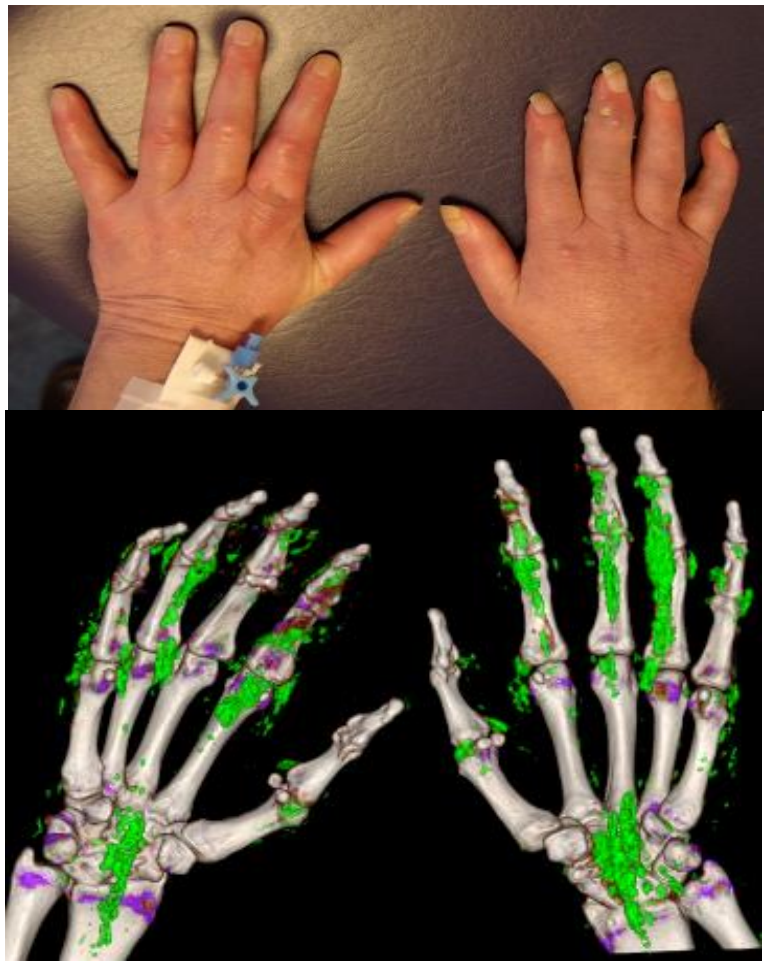


Feet

In a DECT study of 40 pts with non-tophaceous gout, 95% had urate deposits present

Bongartz T, et al. *Ann Rheum Dis.* 2014;74:1072-1077.

Urate burden extends beyond visible tophi



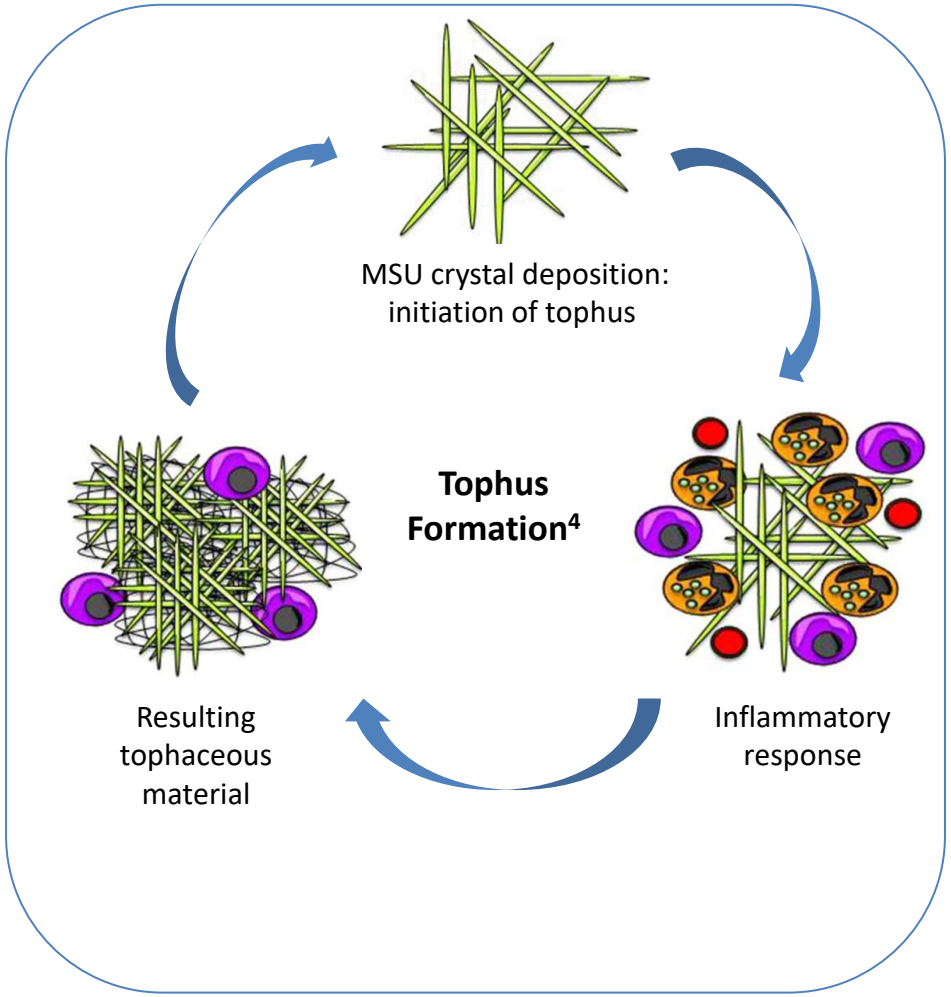
Deposition of MSU crystals detected using DECT (displayed in green). Images courtesy of Dr. Jürgen Rech. Individual patient presentations may vary.

- In addition to visible tophi, MSU crystals can accumulate anywhere in the body except the brain
- In a study of 20 patients with gout, significant differences in urate deposits were detected with dual-energy computed tomography (DECT) versus physical examination
  - Only 25% of tophi were detected on physical exam versus DECT

All gout is technically tophaceous

- Systemically, urate crystal deposition initiates the formation of a tophus
- Gout patients are tophaceous by the time the first attack occurs
- Tophi start as small monosodium urate (MSU) aggregates that can only be visualized microscopically

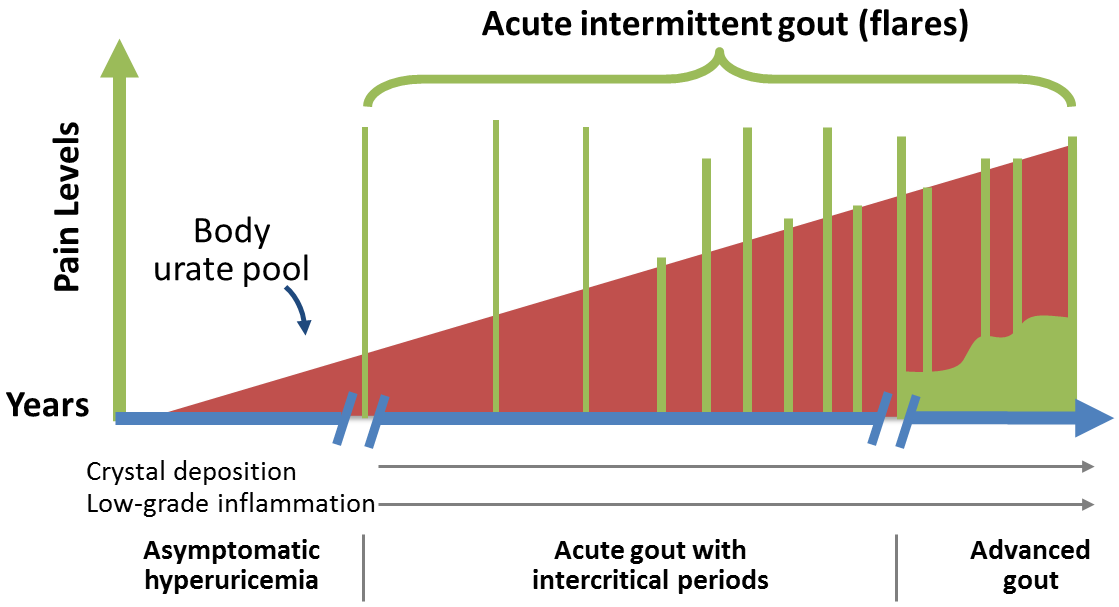
Tophi formation can occur throughout the body, including in organs

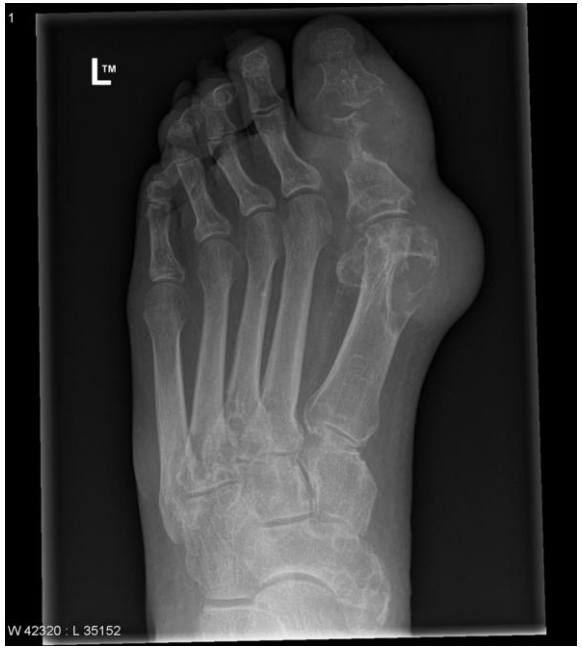


Schett G, et al. *RMD Open*. 2015;1:e000046.11

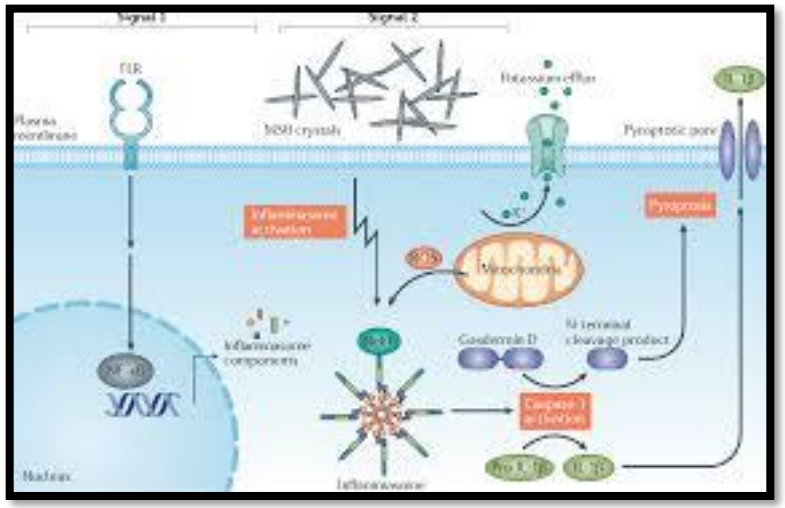
Mysteries of gout

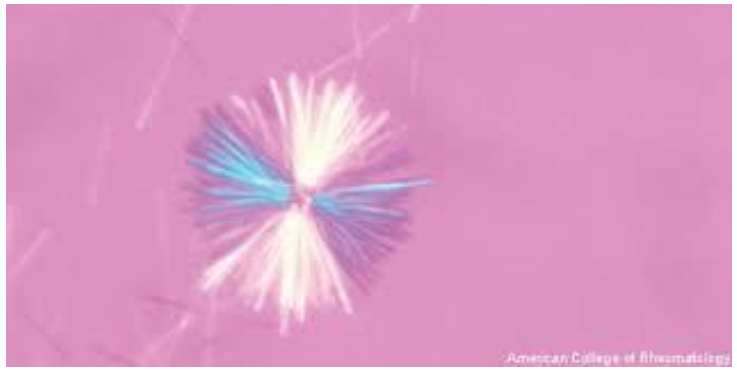
- How do MSU crystals incite an inflammatory response?
- Why are gout flares self-limiting?
- How do erosions form in the absence of chronic pain?

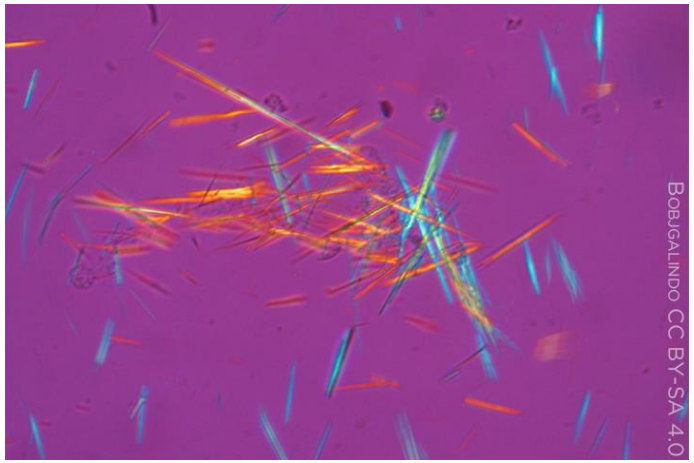




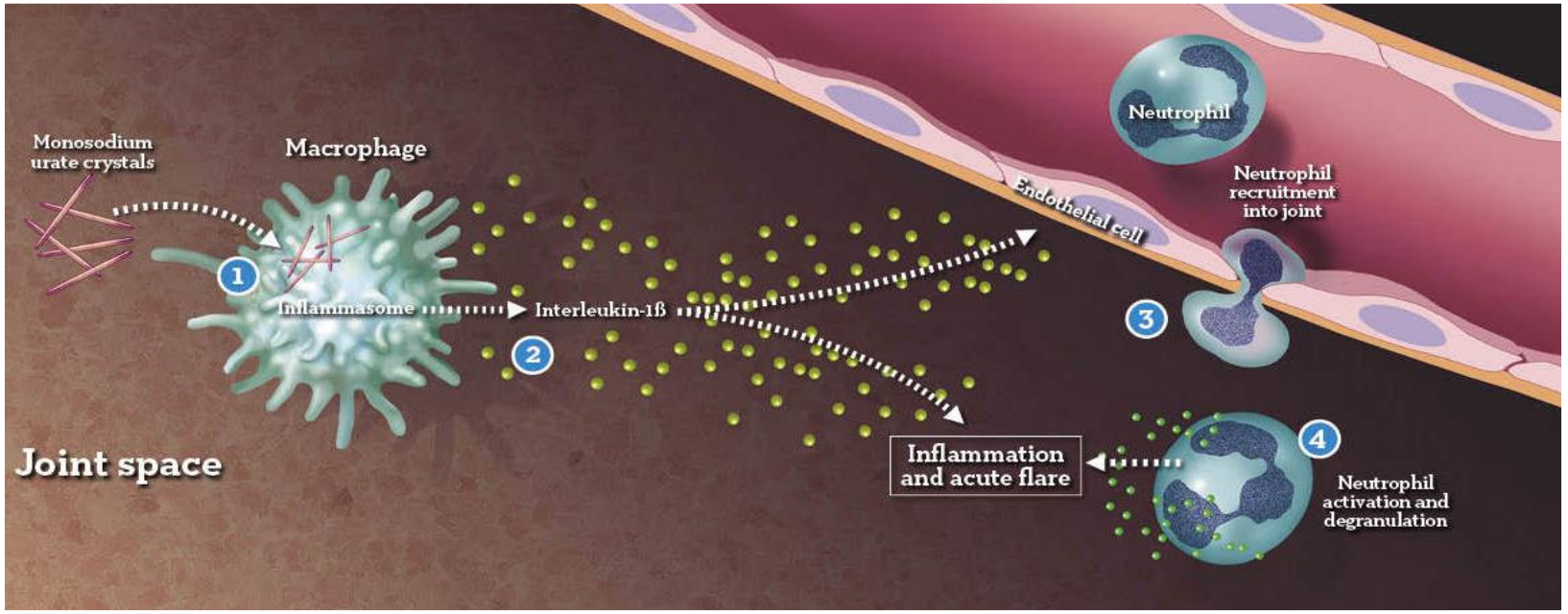
The Immunopathology of Gout







Crystal-induced systemic inflammation



1. Macrophages take in MSU crystals and release inflammatory cytokines like IL-6

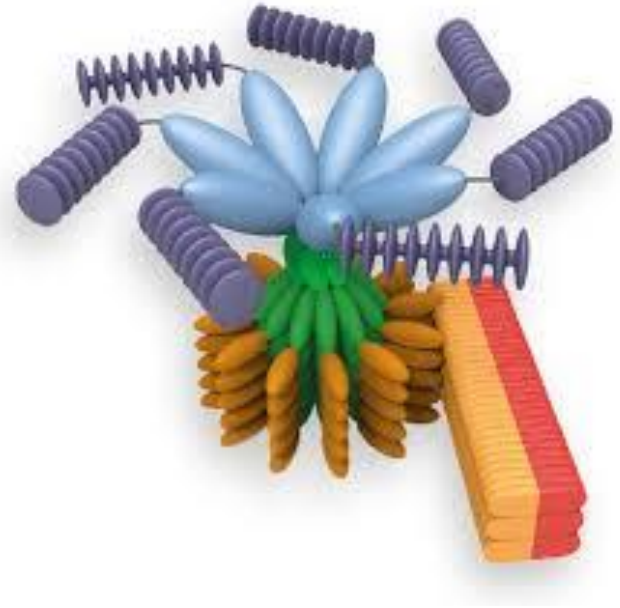
2. Activation of NLRP3 Inflammasome triggers IL-1ß

3. Release of IL-1ß triggers neutrophil recruitment and extravasation into the joint space

4. Neutrophil activation leads to the release of more proinflammatory compounds and activates NETosis

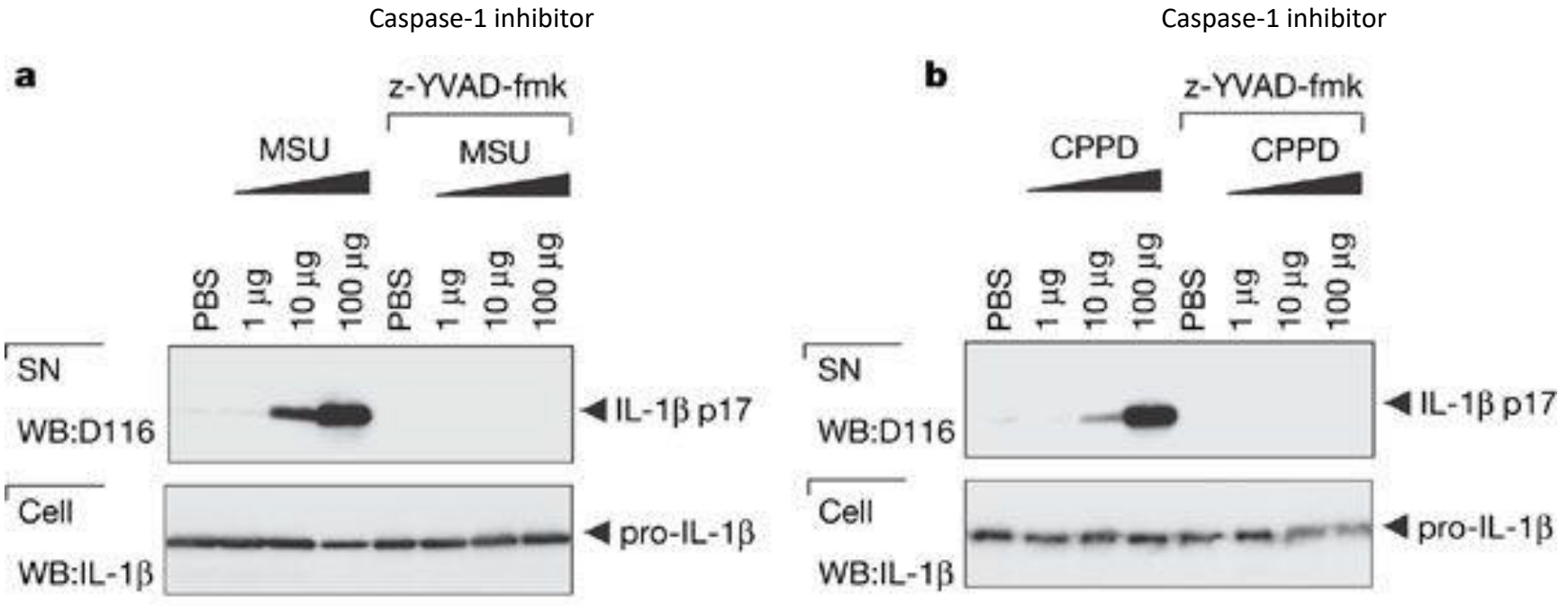
NLRP3 inflammasome

- A macromolecular complex that plays a fundamental role in autoinflammatory diseases
- Key regulator of innate inflammatory responses
- Processes pro-inflammatory cytokine IL-1β
- Implicated in several diseases:
  - gout
  - pseudogout
  - type 2 diabetes mellitus
  - periodic fever syndromes: Muckle-Wells syndrome (MWS), familial cold autoinflammatory syndrome (FCAS), neonatal onset multisystem inflammatory diseases (NOMID)



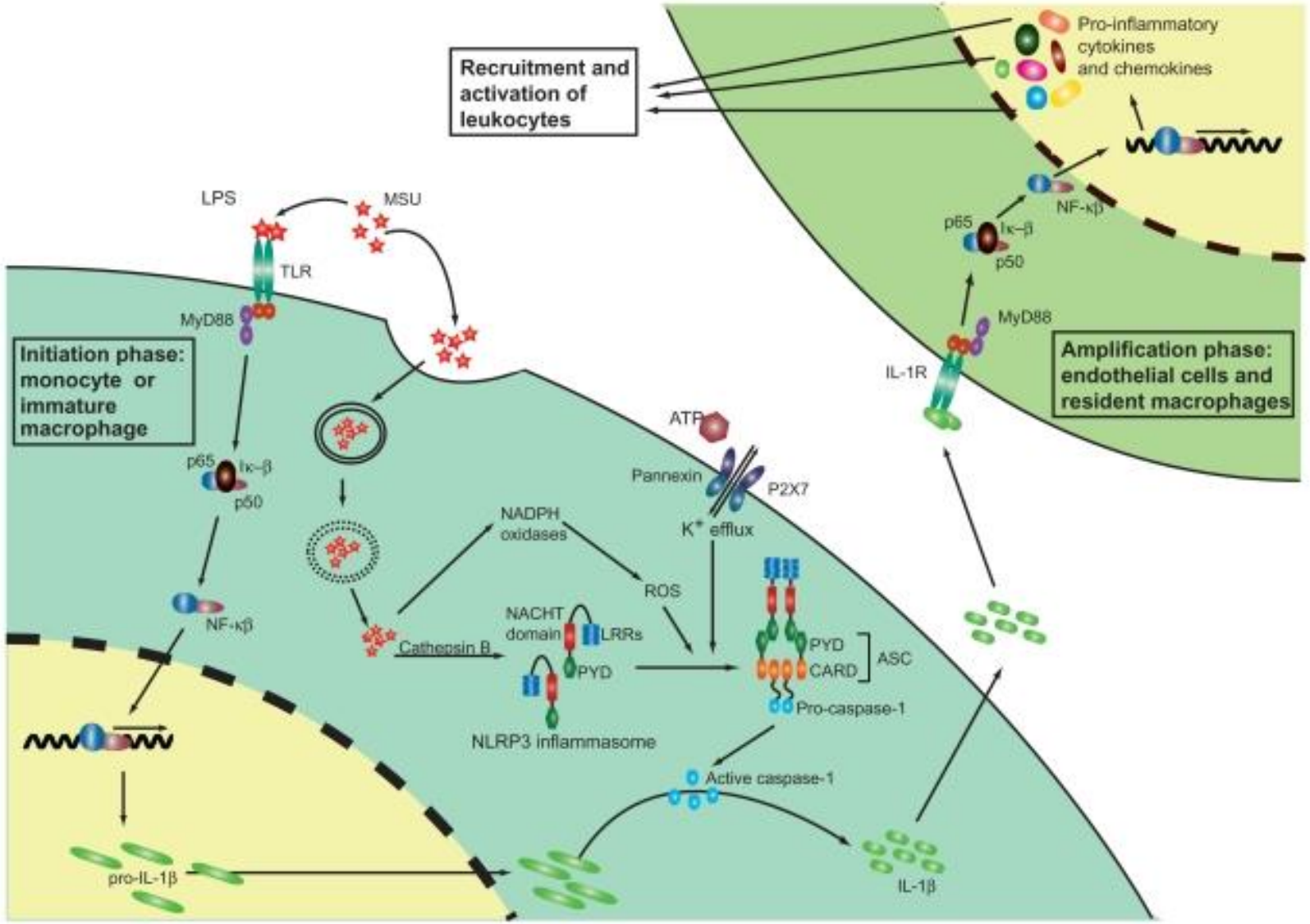
Gout (& pseudogout) are autoinflammatory diseases

MSU and CPPD crystals activate the
NLRP3 inflammasome to express IL-1β



Martinon F, et al. *Nature* 2006; Mar 9;440(7081):237-41.

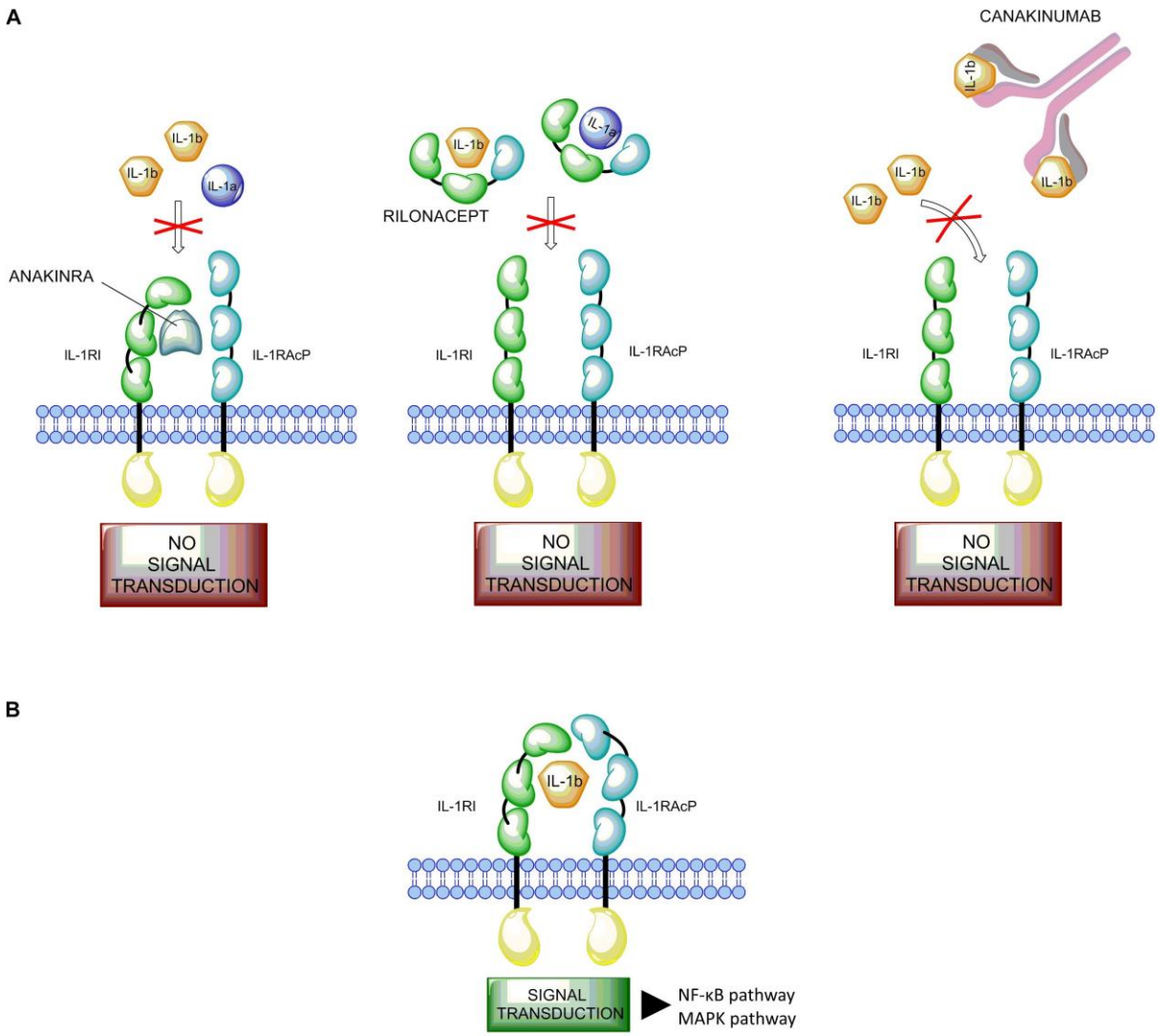
NLRP3 inflammasome



Kingsbury SR, et al. *J Inflamm Res*. 2011; 4: 39-49

Treatment implications: IL-1 inhibitors for gout

- anakinra (Kineret):
  IL-1 receptor antagonist
- rilonacept (Arcalyst):
  IL1 trap
- canakinumab (Ilaris):
  IL-1 mAb
- none are FDA-approved for the treatment of gout
- may also be effective in pseudogout (CPPD deposition disease)



Inhibition of IL-1 as a treatment for gout

anakinra

- Open-label pilot studies: anakinra 100 mg daily improved symptoms
- Phase II RCT: anaGO (Birmingham)

rilonacept

- 1 RCT failed to show efficacy in treatment of acute gout flares
- 4 RCTs showed efficacy in preventing mobilization flares when starting urate-lowering therapy

canakinumab

- 3 RCTs showed efficacy in treatment of acute gout flares
- 1 RCT showed efficacy in preventing mobilization flares when starting urate-lowering therapy
- 2014 Cochrane Review: Moderate-quality evidence that canakinumab 150 mg relieved acute gout flare pain better than triamcinolone acetonide 40 mg IM

IL-1 inhibitor not approved by FDA for gout

ARTHRITIS
ADVISORY COMMITTEE MEETING

JUNE 21, 2011

June 21, 2011 – FDA Arthritis Advisory Committee voted 11-1 against approval of canakinumab for treatment of acute gout flares in patient who didn't respond to NSAIDS or colchicine

- Agreed that canakinumab was effective
- But had unanimous concerns for safety: Infection, CV risks, renal risks, pharmacokinetics in elderly
- Study critiques: 6-month follow-up time too short; 43 patients studied too small; subjects didn't reflect clinical practice (young age, lack of typical comorbidities like CKD, diabetes, transplant)

NLRP3 inflammasome and IL-1 are implicated in autoinflammatory diseases

- NLRP3 was previously called cryopyrin
- Cryopyrinopathies: a spectrum of autoinflammatory diseases caused by mutations in NLRP3 that lead to excessive IL-1β production
  - Familial Mediterranean Fever (FMF)
  - TNF Receptor-Associated Periodic Syndrome (TRAPS)
  - Hyperimmunoglobulin D with Periodic Fever Syndrome/Mevalonate Kinase Deficiency (HIDS)
- Common clinical manifestations :
  - Periodic fevers
  - Arthralgias/arthritis
  - Rash
  - Serositis
  - Aphthous ulcers

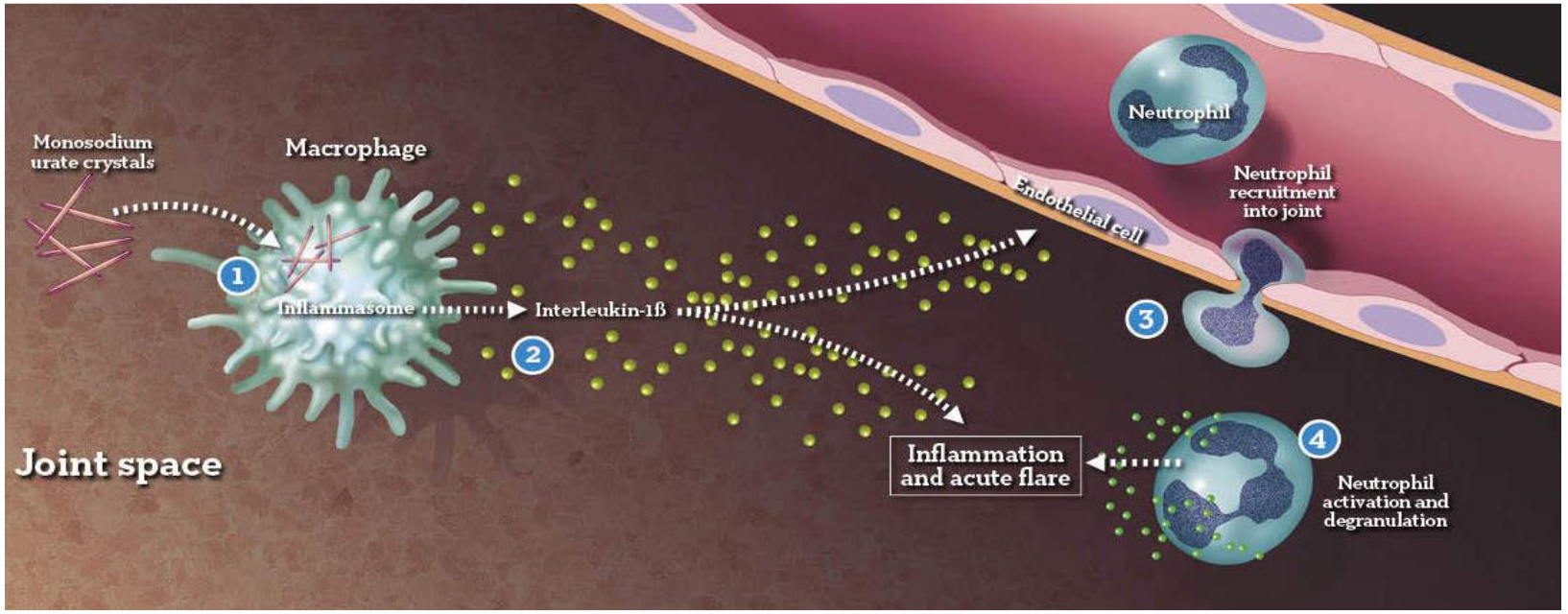
NLRP3 inflammasome and IL-1 are implicated in autoinflammatory diseases

- The same mechanism of IL-1 upregulation via the NLRP3 inflammasome occurs in gout and autoinflammatory diseases

- Current indications of IL-1 inhibitors:
  - Kineret (anakinra): RA, NOMID
  - Arcalyst (rilonacept): CAPS (FCAS, MWS), recurrent pericarditis
  - Ilaris (canakinumab): CAPS, TRAPS, HIDS, FMF

- Gout is an autoinflammatory disease

Crystal-induced systemic inflammation



1. Macrophages take in MSU crystals and release inflammatory cytokines like IL-6

2. Activation of NLRP3 Inflammasome triggers IL-1ß

3. Release of IL-1ß triggers neutrophil recruitment and extravasation into the joint space

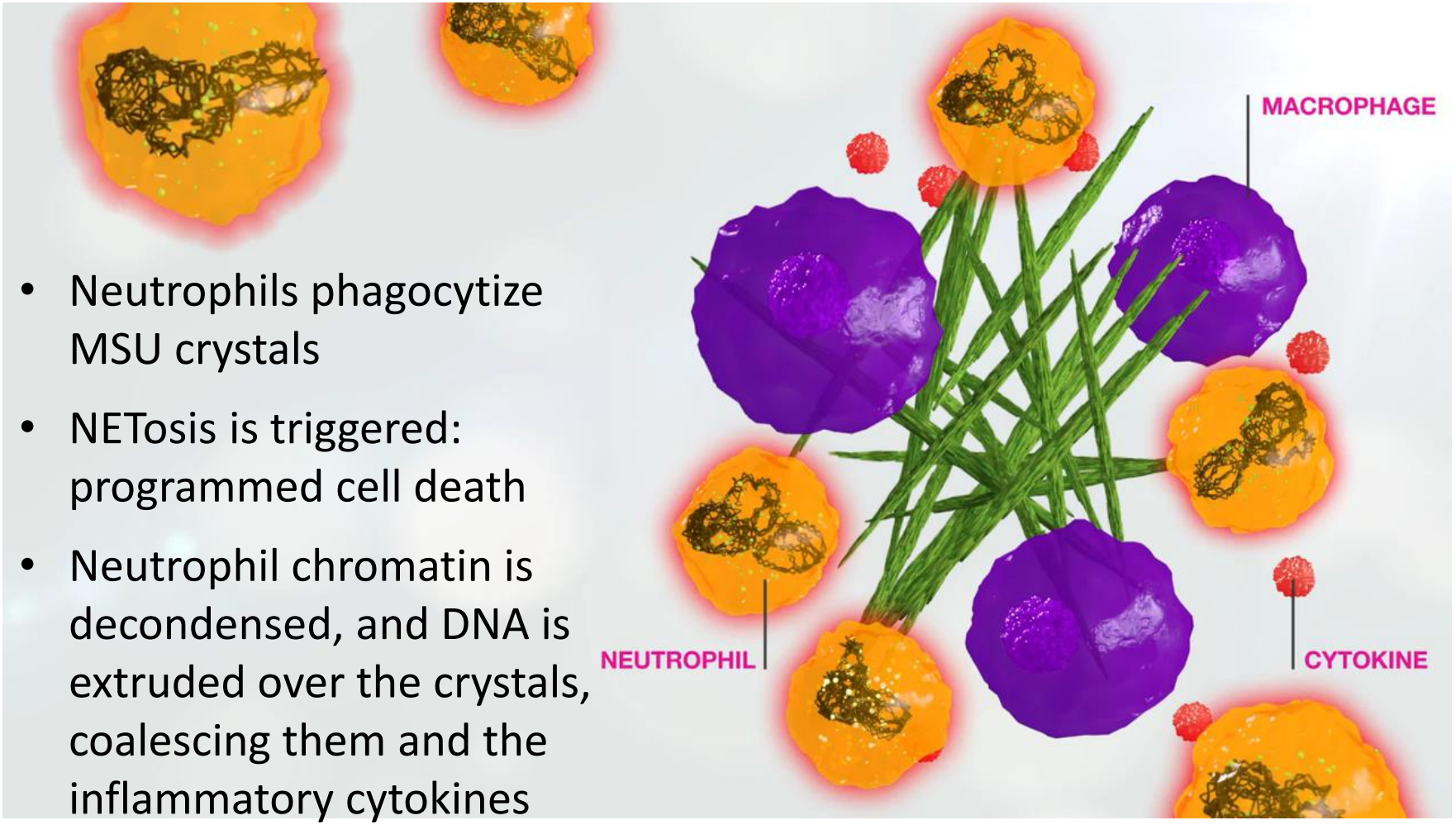
4. Neutrophil activation leads to the release of more proinflammatory compounds and activates NETosis

Innate inflammatory response in gout

- Monosodium urate crystals activate the NLRP3 inflammasome
- IL-1β is upregulated
- Macrophages are induced to release cytokines, like IL-6
- Neutrophils are recruited to mediate the innate inflammatory response

Neutrophil extracellular traps in gout: NETosis

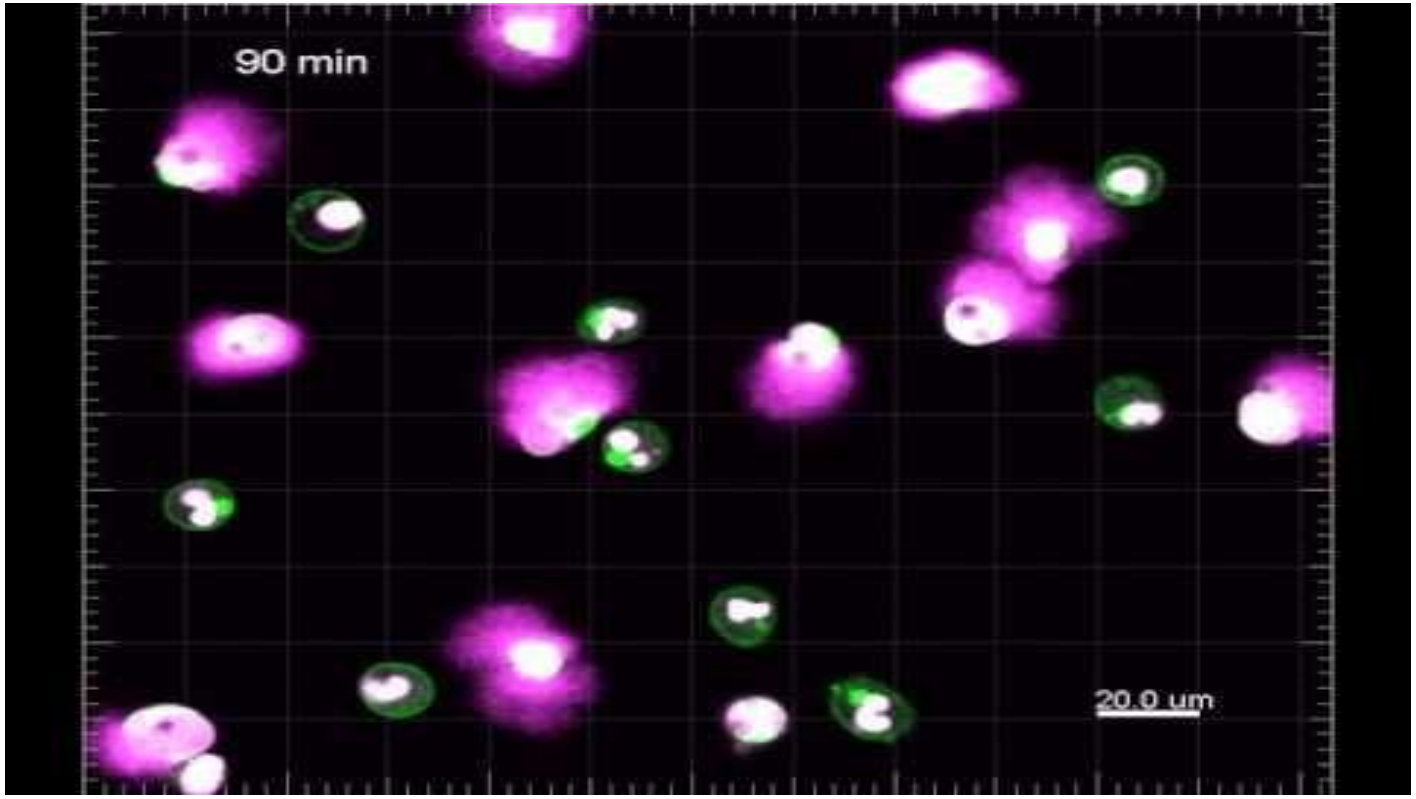
- Neutrophils phagocytize MSU crystals
- NETosis is triggered: programmed cell death
- Neutrophil chromatin is decondensed, and DNA is extruded over the crystals, coalescing them and the inflammatory cytokines



Neutrophil extracellular traps in gout: NETosis

- Proteolytic enzymes are released, cleaving cytokines (e.g. IL-6) and mitigating pain and inflammation
- The densely packed MSU crystals form aggNETs, which rapidly resolve the gout flare

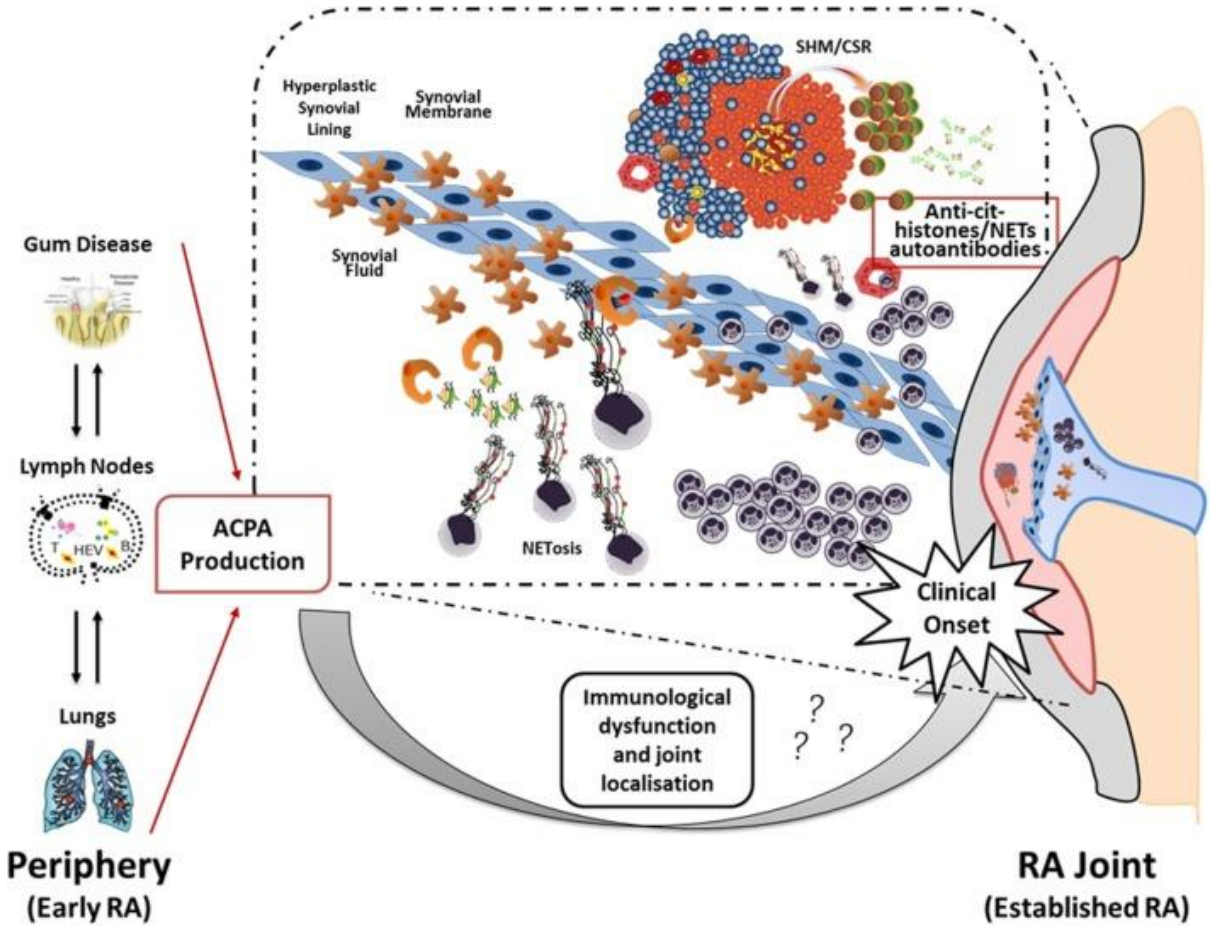
NETosis



NETosis

- NETs have been demonstrated in infection, malignancy, atherosclerosis, and rheumatic diseases
  - Rheumatoid arthritis
  - Systemic lupus erythematosus
  - ANCA-associated vasculitis
  - Psoriasis
  - Gout
- NETs are source of autoantibodies
- NETs release peptidyl arginine deiminase-2 and -4 (PAD2 and PAD4), which promote citrullination in RA
- SLE patients have a decreased ability to degrades NETs

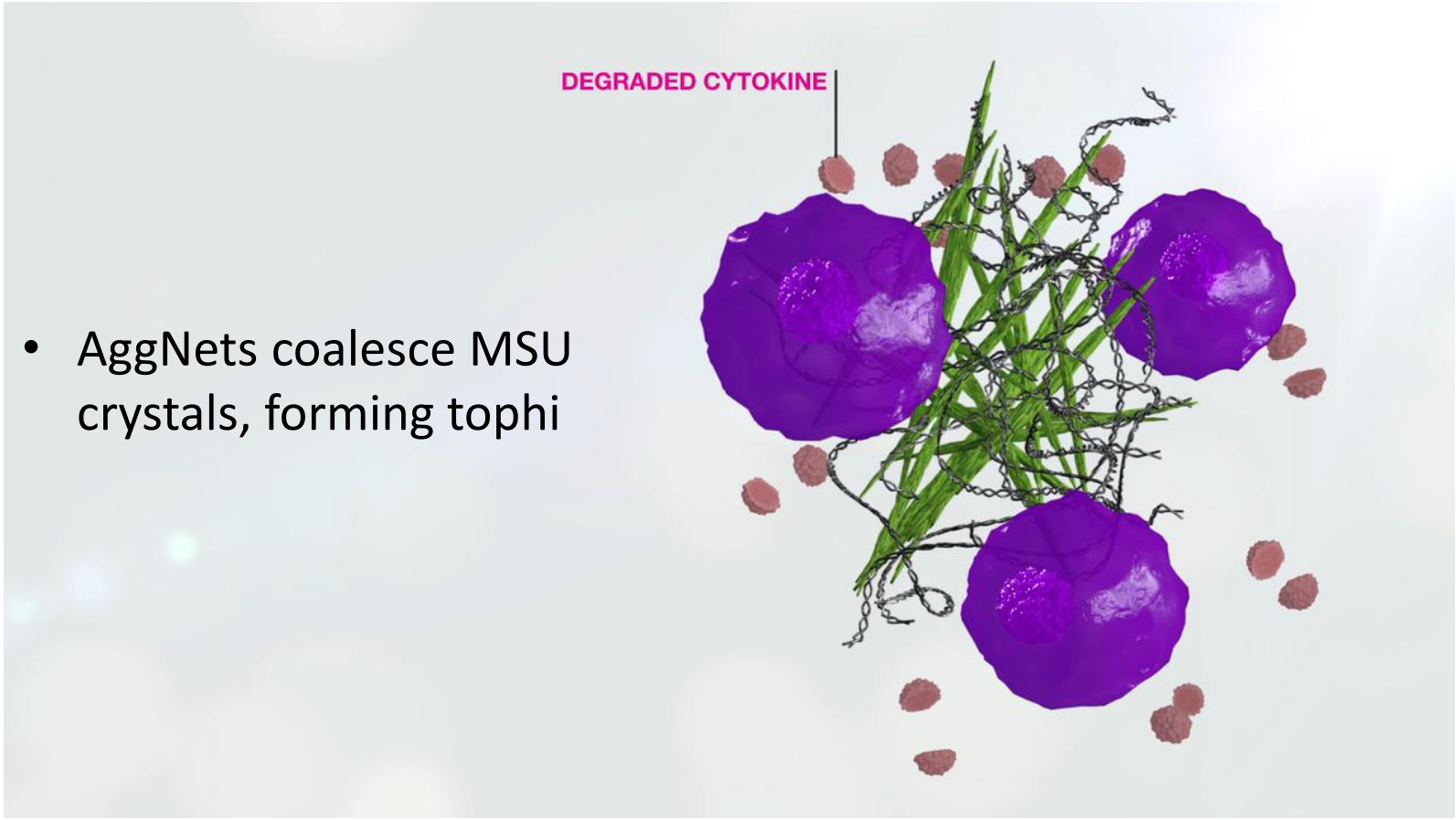
NETosis: A key pathogenic process in autoimmune diseases and gout



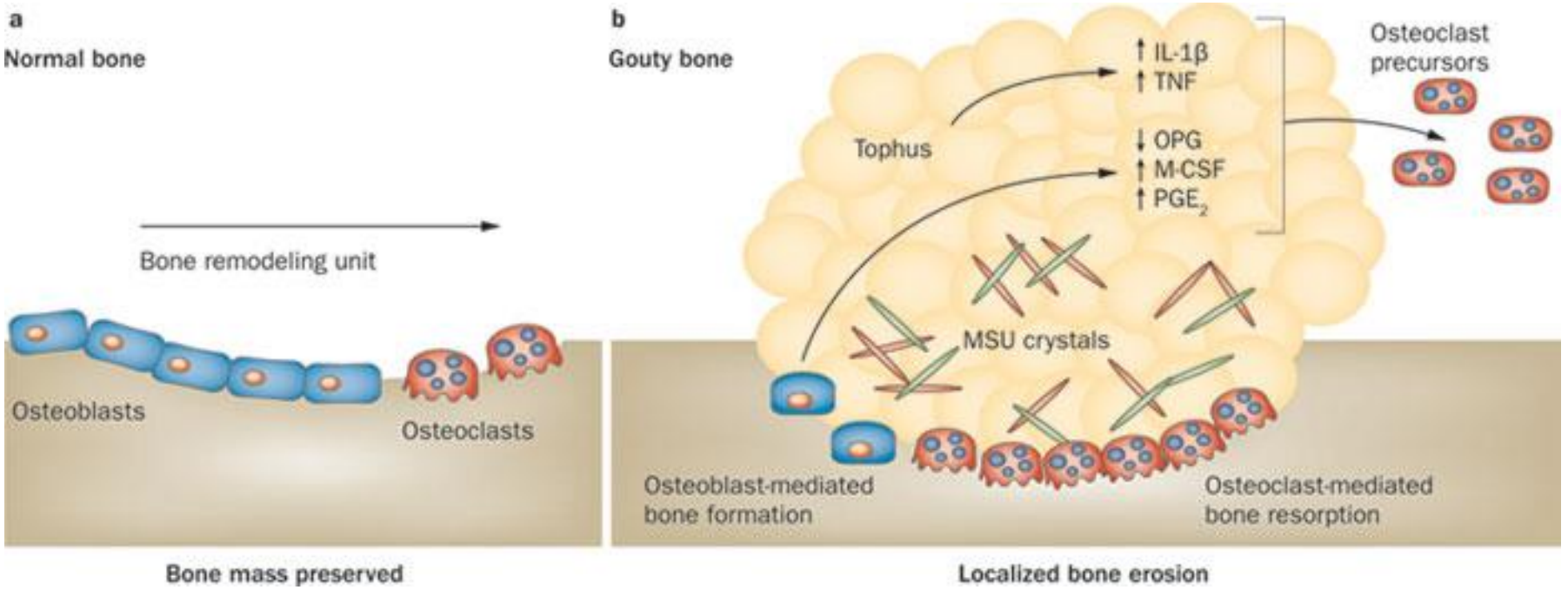
NETosis provides a continuous source of autoantigen that perpetuates chronic inflammation and autoimmunity

Tophi

- AggNets coalesce MSU crystals, forming tophi



Tophi disrupt bone homeostasis to cause bone erosion



McQueen, F.M. et al. Nat. Rev. Rheumatol. 8, 173–181 (2012)

- Urate crystal deposition can lead to inflammation and shifts the balance of osteoblasts:osteoclasts
- Tophi can lead to destructive skeletal changes via similar mechanisms as osteoporosis

Anti-resorptive and anabolic bone agents as treatments for gout

- RCT: Bisphosphonates failed to prevent the development of erosions in patients with long-standing tophaceous gout

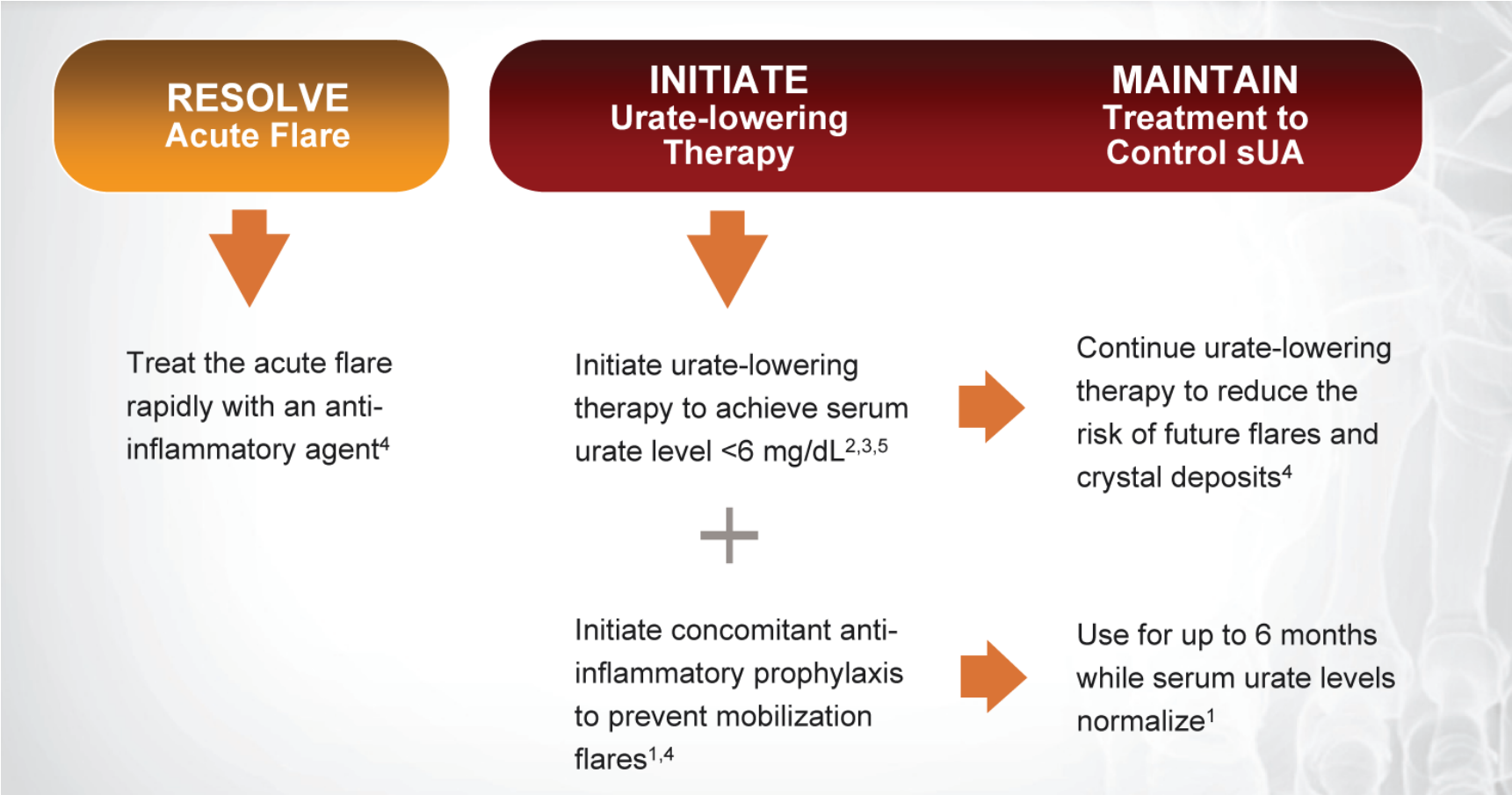
  Dalbeth N, et al. Ann Rheum Dis 2014;73:1044-1051.

- Active Phase II RCT: Denosumab In Addition To Intense Urate-Lowering Therapy for Bone Erosions (Birmingham)

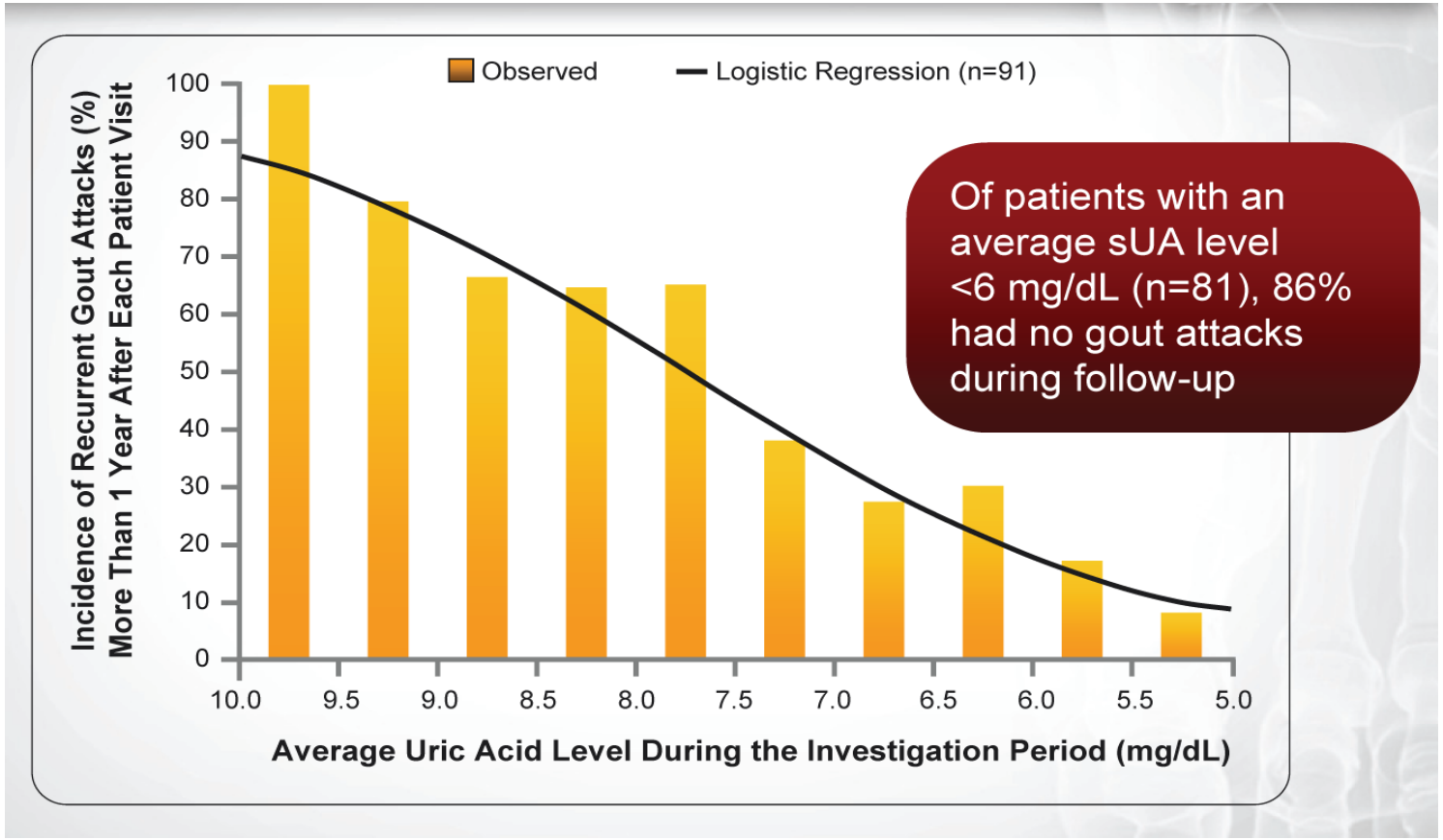
- No active clinical trials investigating teriparatide, abaloparatide, or romosozumab

Current Treatment Approaches for Gout

Gout management approach

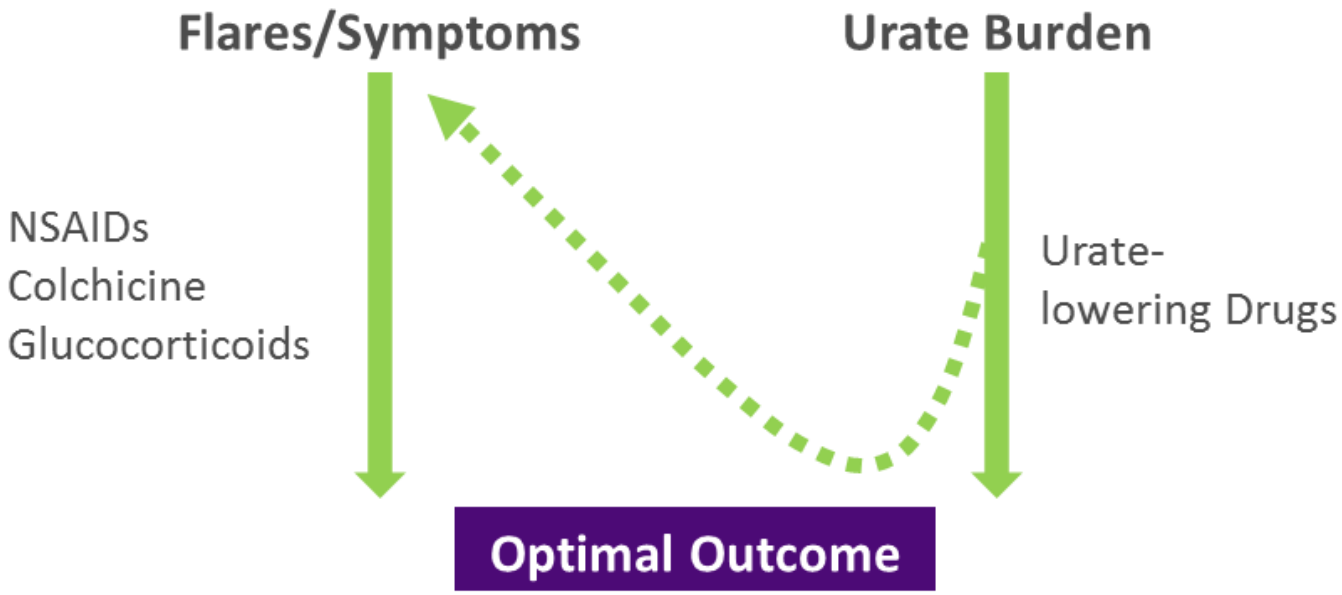


Maintaining SUA <6 mg/dL is associated with reduced risk of recurrent gout flares



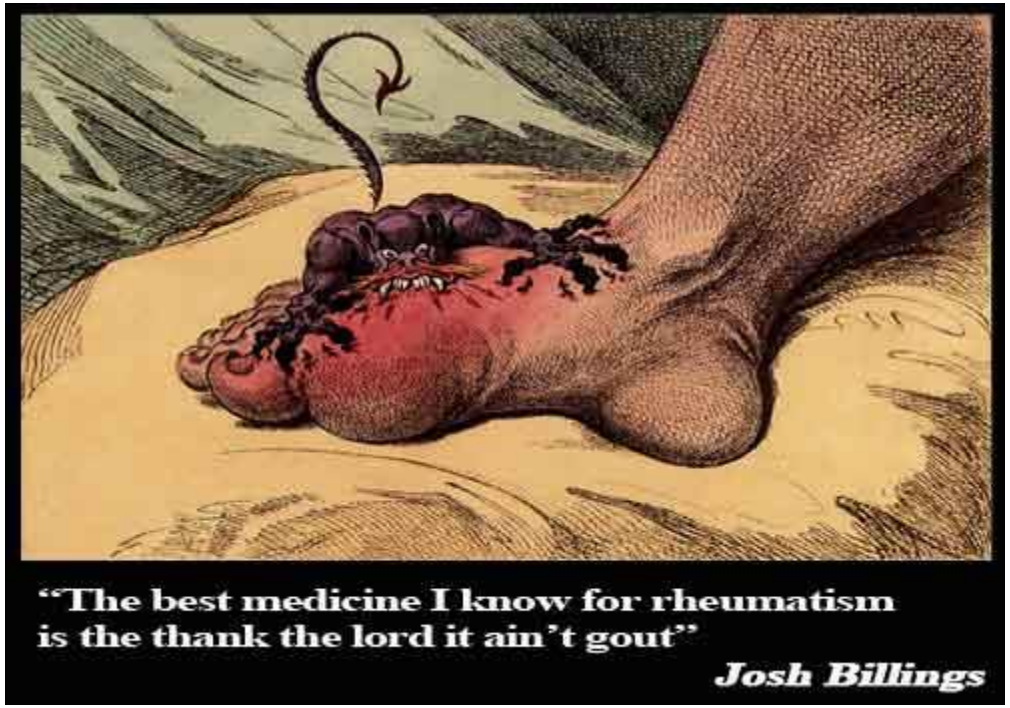
Appropriate Management of Gout Requires Control of Both Symptoms and Urate Burden

- In order to achieve optimal patient outcomes, it is important to address 2 processes simultaneously
  - Controlling flares and symptoms
  - Reducing the excess body burden of urate



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

Treatment of gout



Current FDA-approved classes of urate-lowering therapies

Small molecules

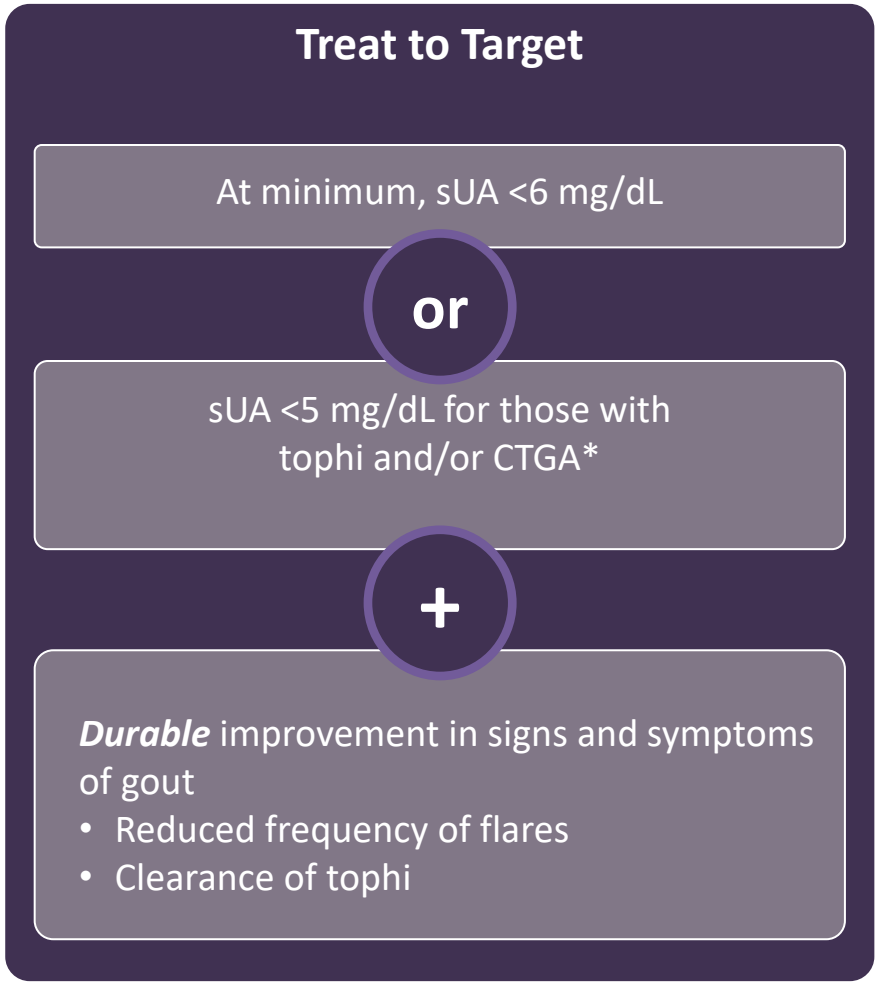
- xanthine oxidase inhibitors
  1. allopurinol
  2. febuxostat
- uricosurics
  1. probenecid
  2. lesinurad

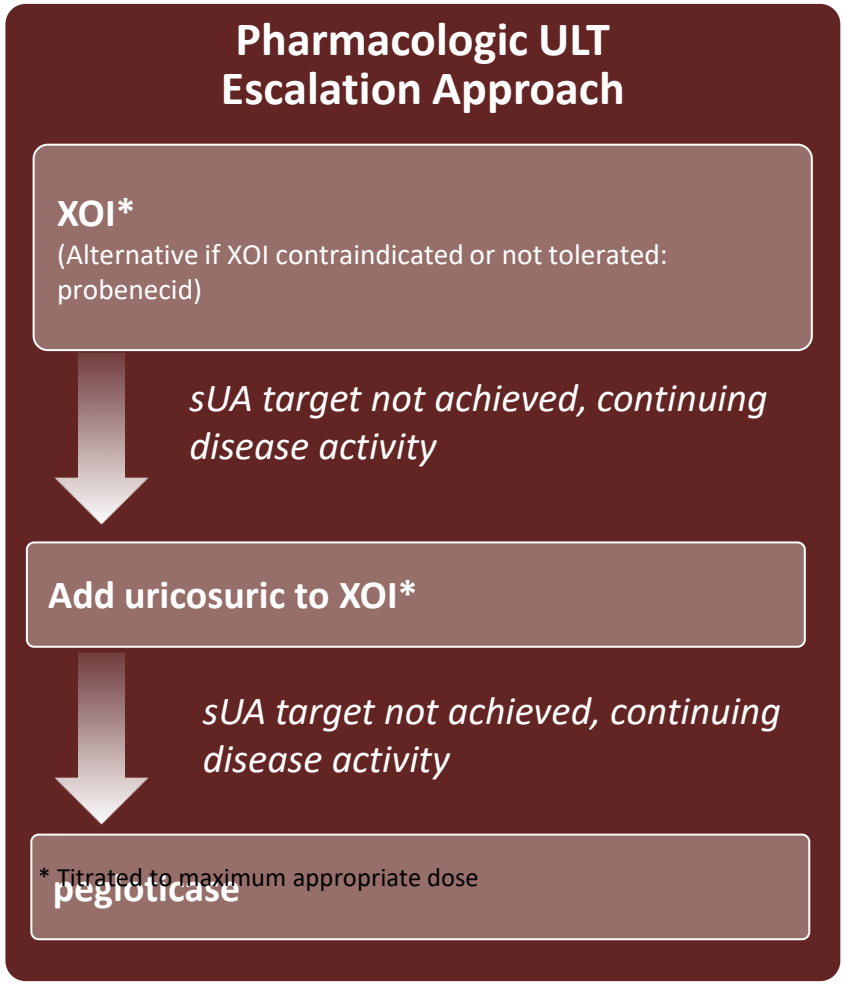
Biologic

- pegloticase

Zurampic (lesinurad) and Duzallo (lesinurad/allopurinol) removed from the US marketplace by the manufacturer [December 2018][2]

2012 ACR Gout Treatment Guidelines





2020 ACR Gout Guidelines Update

FitzGerald JD, et al. *Arthritis Rheumatol*. 2020;72:879-895.

- " … intended to provide guidance for particular patterns of practice and not to dictate the care of a particular patient"
- Provided an update from the 2012 guidelines using additional evidence that form the basis of directing care
- 42 recommendations, 16 of which are rated as *strong*
  - When to initiate urate-lowering therapy
  - Treat-to-target of <6 mg/dL
  - Prophylaxis against attacks
  - Allopurinol as first choice urate-lowering therapy (ULT)
  - Avoiding hypersensitivity reactions
  - Modifying non-gout medications
  - Use of pegloticase
  - Treating flares

2020 ACR Gout Guidelines – Indications for pharmacologic ULT

For patients with asymptomatic hyperuricemia (SU >6.8 mg/dL with no prior gout flares or subcutaneous tophi), we conditionally recommend *against* initiating any pharmacologic ULT (allopurinol, febuxostat, probenecid)

- Certainty of evidence: High
- The presence or absence of uric acid deposits were also not considered
  - ?urolithiasis, intra-organ tophi, intra-arterial deposition?
  - All gout is tophaceous
- However, systemic comorbidities were not considered (e.g., CKD, HTN, CAD, DM)
- Goal of therapy should be to prevent manifestations of disease (flares), as well as sequelae of advanced disease

FitzGerald JD, et al. Arthritis Rheumatol. 2020;72:879-895.

2020 ACR Gout Guidelines – Indications for pharmacologic ULT

We strongly recommend initiating ULT over no ULT for patients:

- with 1 or more subcutaneous tophi (certainty of evidence: High)
- with radiographic damage attributable to gout (certainty of evidence: Moderate)
- with frequent gout flares (>2/year); (certainty of evidence: High)

- Rationale that subcutaneous tophi and erosions represent worse disease activity and prognosis
- Threshold of >2/year was arbitrary
- Decision of when to initiate ULT should be individualized and part of a shared-decision process

FitzGerald JD, et al. Arthritis Rheumatol. 2020;72:879-895.

2020 ACR Gout Guidelines – Recommendations for initial ULT

For patients starting any ULT, we strongly recommend allopurinol over all other ULT as the preferred first-line agent for all patients, including those with CKD stage ≥3.

- The Voting panel preferred allopurinol based partly on safety concerns and cost

For allopurinol and febuxostat, we strongly recommend starting at a low dose with subsequent dose titration to target over starting at a higher dose (e.g., ≤100 mg for allopurinol or ≤40 mg for febuxostat)

- Slow dose-escalation of ULT leads to
  - lower incidence of mobilization flares
  - Decreased risk of allopurinol hypersensitivity syndromes

FitzGerald JD, et al. Arthritis Rheumatol. 2020;72:879-895.

Treatment considerations : Allopurinol

Allopurinol severe cutaneous adverse reactions (SCAR)

- Risks of SCAR with allopurinol = 0.1 – 0.4%
- Mortality rate of up to 25%
- Can occur days, months, or years after drug initiation
- Variants include
  - Stevens-Johnson syndrome (SJS)
  - toxic epidermal necrolysis (TEN)
  - drug reaction with eosinophilia & systemic symptoms (DRESS)
- Risk factors:
  - female
  - age > 60 years
  - CKD stage 4
  - allopurinol starting dose >100 mg daily
  - high-risk ethnicity: non-white, non-Hispanic, HLA-B*5801

Allopurinol genetic screening

HLA-B*58:01 allele is strongly associated with SCAR during treatment with allopurinol

- OR = 73 among HLA-B*58:01 carriers vs health controls
- mechanism involves autoreactivity of cytotoxic (CD8+) T cells

Prior to initiation, test HLA-B*58:01 allele for certain populations

- prevalence rates by ethnicity:

  Han Chinese: 10-15%
  Europeans, Hispanics, and Japanese: 1-2%
  Korean: 12%
  Thai: 6-8%

- testing may not be cost-effect for low-incidence populations

We conditionally recommend testing HLA-B*5801 prior to starting allopurinol for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and African American Patients.
We conditionally recommend against HLA-B*5801 testing in all others

FitzGerald JD, et al. Arthritis Rheumatol. 2020;72:879-895.

Treatment considerations : Allopurinol vs. Febuxostat

CARES trial: Cardiovascular Safety of Allopurinol vs Febuxostat in Patients with Gout

White WB, et al. NEJM.2018;378(13):1200-1210

- 6200 patients with gout and CV disease, randomized to allopurinol or febuxostat (no control group)
- No difference between groups seen in primary endpoint of composite CV events (CV death, nonfatal MI, nonfatal stroke, or unstable angina)
  - HR 1.03 [95% CI, 0.87 to 1.23]
- Interestingly, signals seen in 2 individual components: CV death and all-cause mortality
  - sudden cardiac death 2.7% in febuxostat vs 1.8% in allopurinol
  - HR for CV death 1.34 [95% CI, 1.03 to 1.73]
  - HR for death from any cause 1.22 [95% CI, 1.01 to 1.47]
- Led to FDA Boxed Warning for Uloric on 2/21/2019

Treatment considerations : Allopurinol vs. Febuxostat

CARES trial caveats:

- 85% of events occurred while patients weren't receiving study drug
- More patients in febuxostat arm were on NSAIDs
- No difference in CV death if patients were taking ASA and were not smokers
- Patients dropped out at high rates (56% stopped meds; 45% lost to follow-up)
  - post-hoc ascertainment added 199 events, which decreased all-cause mortality HR to 1.09 [95% CI, 0.94 to 1.28]

Treatment considerations : Allopurinol vs. Febuxostat

CARES trial critical appraisal:

- Findings difficult to interpret in setting of no difference in other composite outcome measures: MI, CVA, unstable angina
- Plausibility questionable as both medications are xanthine oxidase inhibitors and act by the same mechanism of action
- No placebo group in trial design (could allopurinol be protective and febuxostat represent no change from untreated?)
- Other trials did not observe increased CV death with febuxostat
- Results valid, but clinical relevance unknown
- Analogous out FDA's drug safety communication on Xeljanz vs. TNFi in RA patients

Treatment considerations : Allopurinol vs. Febuxostat

FAST trial: Long-term CV safety of febuxostat and allopurinol in patients with gout

Mackenzie IS, et al. Lancet.2020;396(10264):1745-57.

- 6128 patients with gout and CV disease, randomized to allopurinol or febuxostat (no control group)
- Febuxostat was non-inferior to allopurinol in primary endpoint of composite CV safet:y hospitalization for non-fatal MI or biomarker-positive ACS; non-fatal stroke; or CV death
  - HR 0.85 [95% CI, 0.70 to 1.03]
- Long-term use of febuxostat is not associated with an increased risk of death or serious adverse events compared with allopurinol.

Effect of the CARES trial and FDA Box Warning may have led to decreased disease control of gout, despite critical appraisal and the follow-up FAST trial.

2020 ACR Gout Guidelines – Treat-to-Target

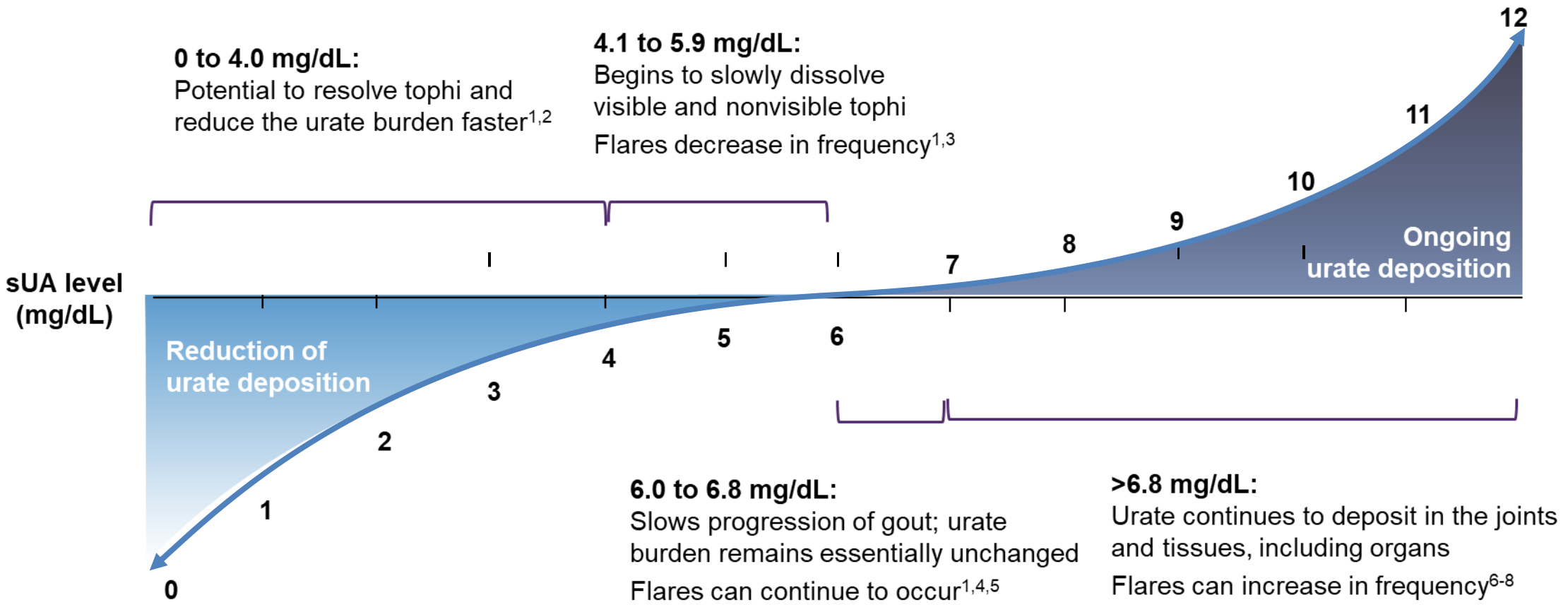
For all patients taking ULT, we strongly recommend continuing ULT to achieve and maintain an SU target to <6 mg/dL over no target

- Specifically meant as a rebuttal to the ACP Gout Treatment Guidelines that advocated a fixed-dose, treat-to-flare approach; *not* a treat-to-target approach

- Removed the 2012 treatment goal of SUA <5 mg/dL for pts with tophi or CTGA because of "lack of supporting evidence for…further thresholds warranting more intensive ULT."

FitzGerald JD, et al. Arthritis Rheumatol. 2020;72:879-895.

Solubility of SUA: Lowering sUA Level Depletes of Urate Burden



Perez-Ruiz F. *Rheumatology (Oxford).* 2009;48(suppl 2):ii9-ii14.

Patients With Uncontrolled Gout Fail to Achieve Target SUA Levels With Oral ULTs

- Becker MA, et al. *N Engl J Med.* 2005;353:2450-2461:
  - 79% of pts (n=251) on 300 mg allopurinol/day x 52 wks did not meet target sUA <6.0 mg/dL
  - 47% of pts (n=255) on 80 mg febuxostat/day x 52 wks did not meet target sUA<6.0 mg/dL

- Sundy JS, et al. JAMA, 2011;306(7): 711-720:
  - In about 200,000 gout patients, conventional oral urate-lowering agents fail to control gout → refractory (uncontrolled) gout

Therefore, a significant treatment gap exists for patients with uncontrolled gout

Definition of Uncontrolled (Refractory) Gout

Symptomatic gout in which conventional urate-lowering therapies are contraindicated or the maximum medically appropriate dosage of these therapies are inadequate

- recurrent and disabling gout flares
- chronic gouty arthropathy with or without bony erosions
- visible progressive tophi
- progressive physical disability
- poor health-related quality of life

The combination of severe gout, high burden of 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

Lesinurad) and lesinurad/allopurinol) removed from the US marketplace by the manufacturer [December 2018]

- 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 approved for the treatment of refractory gout

- pegloticase is a uric acid-specific enzyme, which is a PEGylated product that consists of recombinant modified mammalian urate oxidase (uricase)
- pegloticase achieves its therapeutic effect by catalyzing the breakdown 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

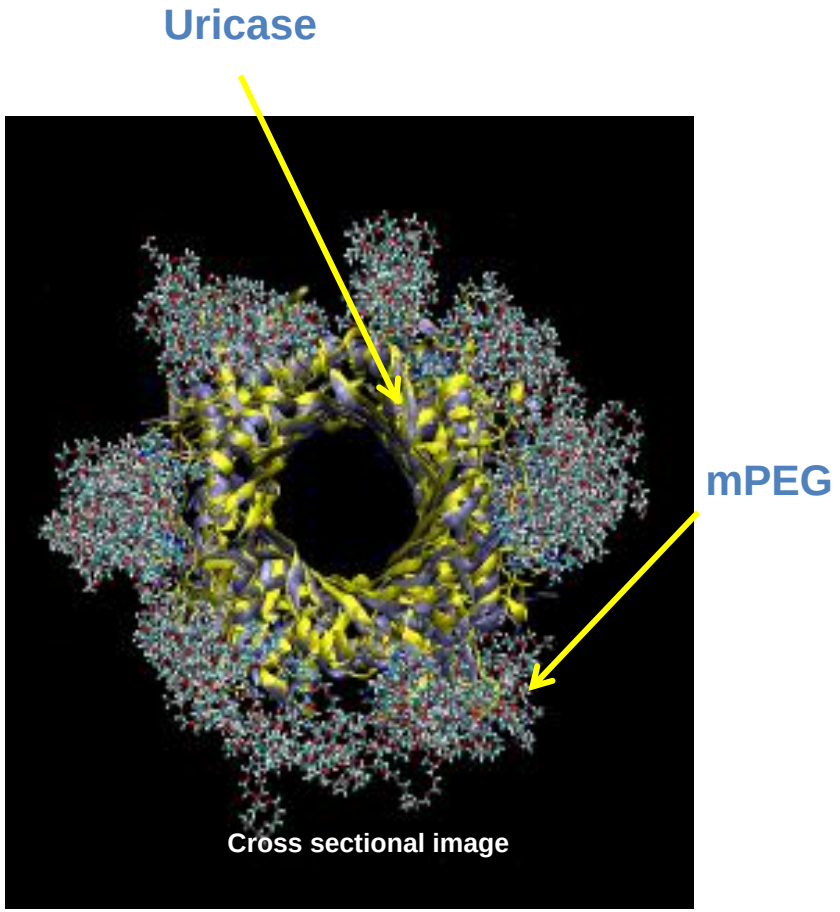
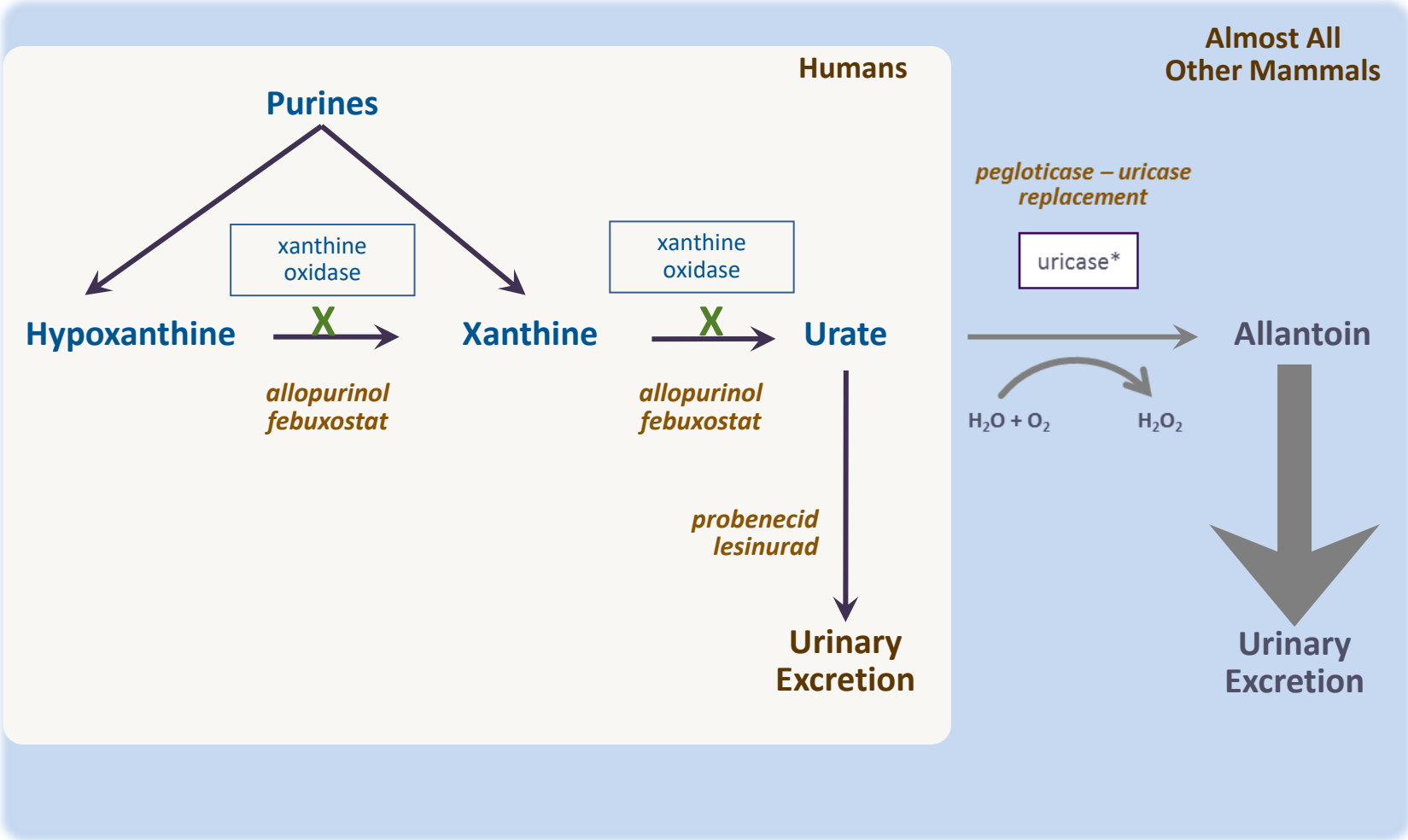
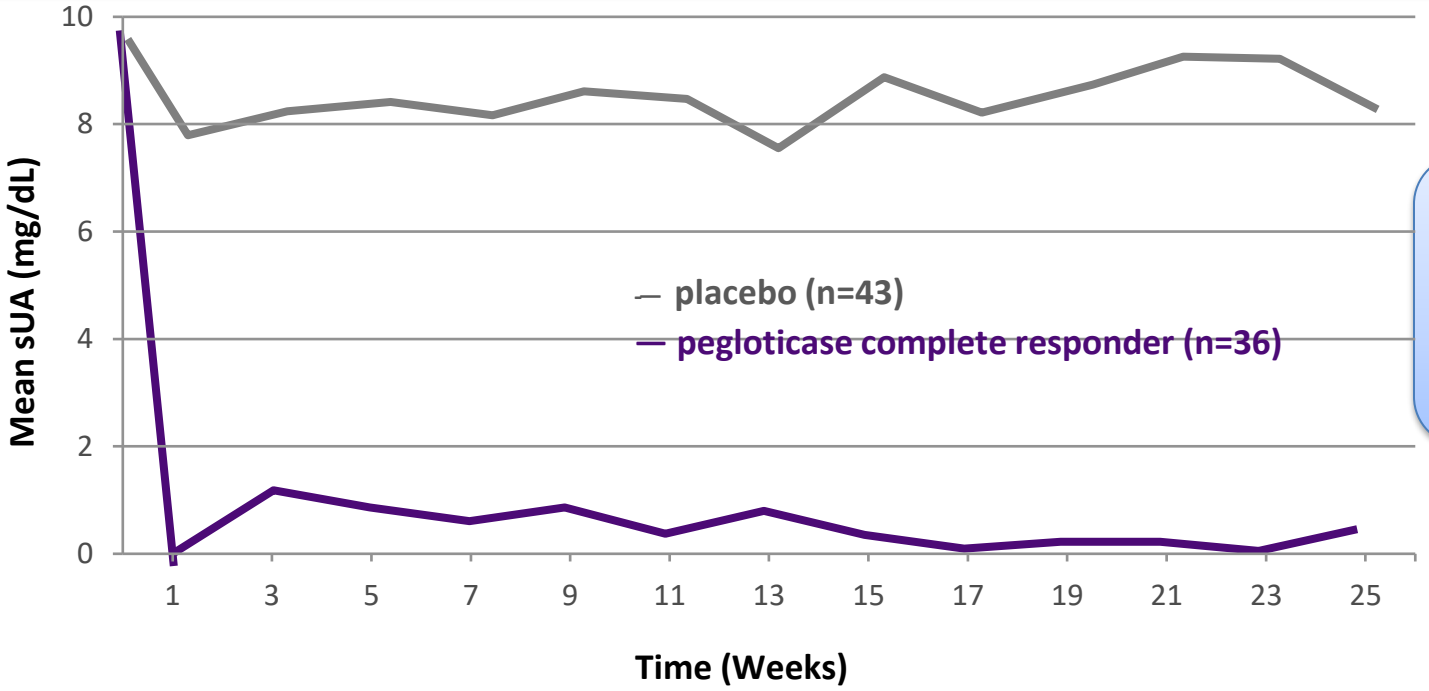


Figure courtesy of Toby Sannan and Christopher Hadad, Ohio State University.

Purine catabolism



Phase III RCTs: Primary endpoint - Complete Responders

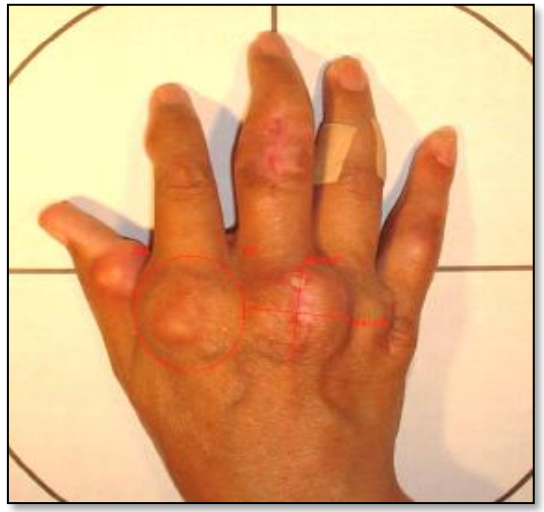
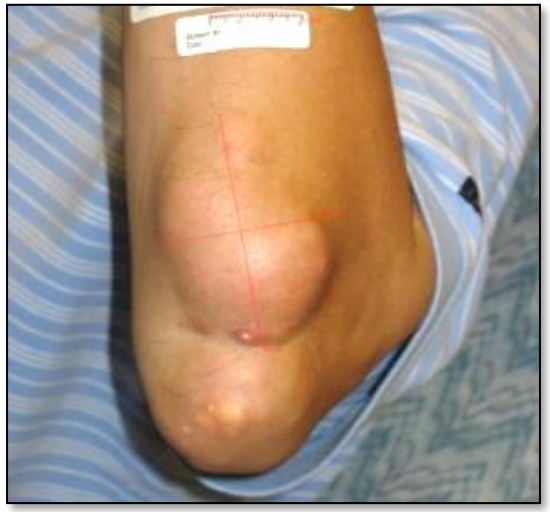
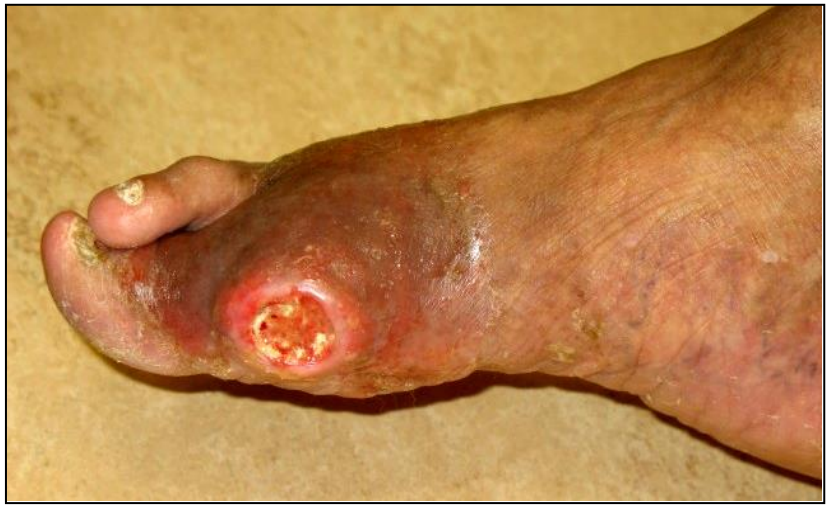
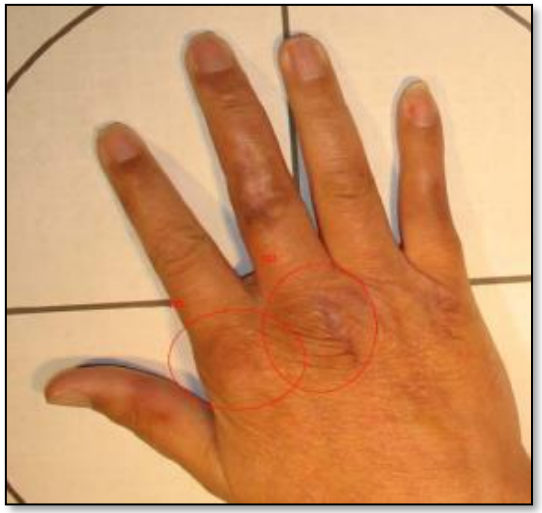
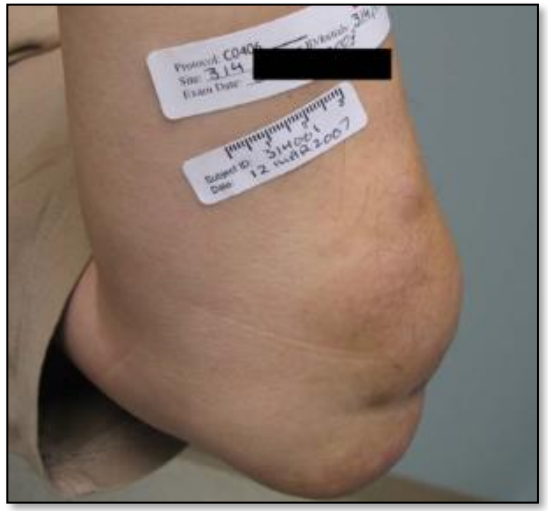
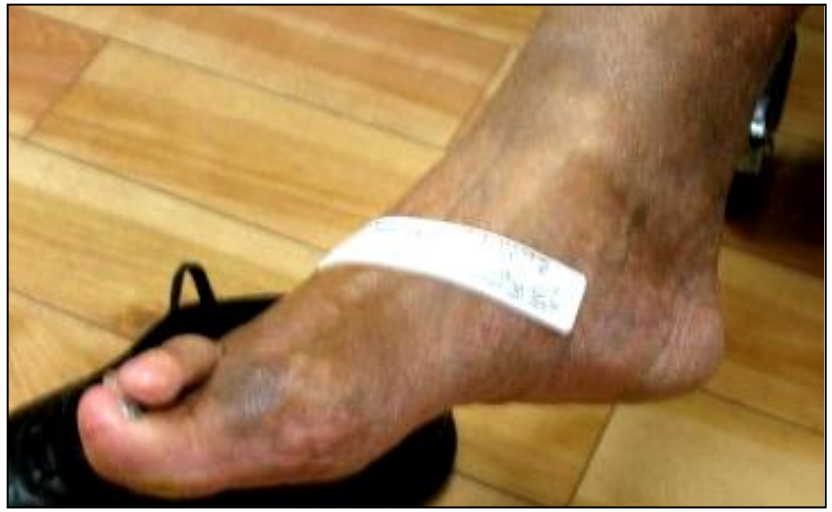


42%

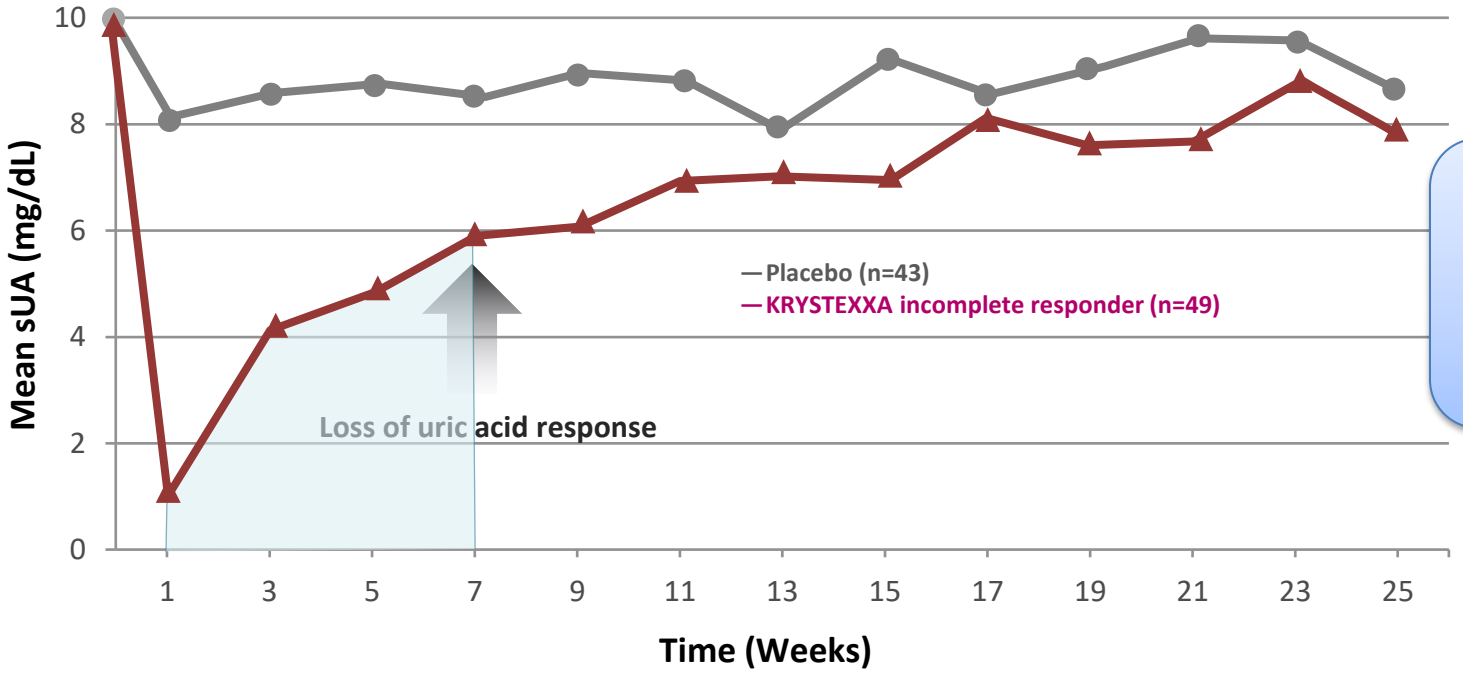
of patients had a complete response

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

Secondary endpoint – Tophus resolution

Pooled Pivotal Trials Results: Incomplete Responders



58%

of patients had an incomplete response

- Loss of response was thought to be due to the formation of anti-drug antibodies to pegloticase
- Anti-drug antibodies may also contribute to infusion reactions
  - 26% infusion reactions
  - 5% severe (classified as anaphylaxis by FDA post-hoc)

Concomitant immunomodulation with pegloticase to decrease immunogenicity

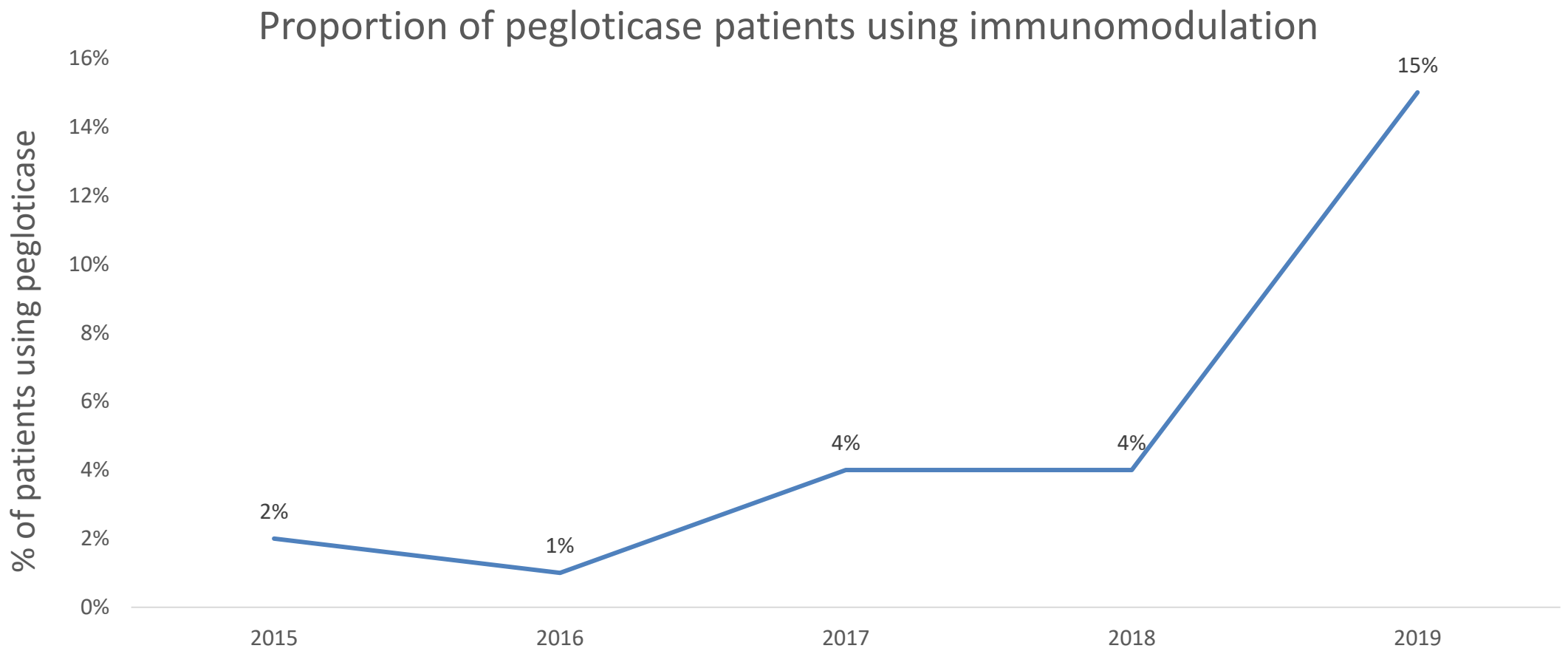
MTX	LEF	AZA	MMF
• Botson J, Peterson J[1,2]	• Masri K, et al[7]	• Berhanu AA, et al[8‡]	• Freyne B[10‡]
• Albert JA, et al[3]		• TRIPLE[9]	• RECIPE RCT[11]
• Bessen MY, et al[4]			
• MIRROR[5]			
• Soloman N, et al[6]			

1. Botson J, Peterson J. *Arthritis Rheumatol*. 2018;70(suppl 10):1408. 2. Botson J, Peterson J. *Ann Rheum Dis.* 2019;78:1289-1290. 3. Albert JA, et al. *Rheumatol Ther*. 2020;7(3):639-648. 4. Bessen MY, et al. *Int J Clin Rheumatol*. 2019; 14(6):238-245. 5. Botson JK, et al. *J Rheumatol*. doi:10.3899/jrheum.200460. 6. Soloman N, Amin M, et al. *Arthritis Rheumatol*. 2020;72(S10):3289-3291. 7. Masri K, et al. *Ann Rheum Dis*. 2020;79(suppl 1):450. 8. Berhanu AA, et al. *Semin Arthritis Rheum.* 2017;46:754-758. 9. Baraf HS, et al. *Arthritis Rheumatol*. 2020;72(S10):1368-1369. 10. Freyne B. *Transplant Proc*. 2018;50:4099-4101. 11. Khanna P, et al. *Arthritis Rheumatol*. 2020;72(S10):1911-1913.

RECIPE RCT: Pegloticase with mycophenolate mofetil

- Double-blind, randomized, multicenter, placebo-controlled clinical trial (N=32)
- Primary endpoint: proportion of patients achieving and maintaining sUA levels ≤6 mg/dL at 12 weeks
- At 12 weeks, MMF was stopped to assess durability of immune modulation after discontinuation
- **86%** of patients (19/22) in the MMF arm maintained sUA levels ≤6 mg/dL at Week 12, compared to 40% in the placebo arm (4/10; *P*=0.01)
- **68%** of patients from the MMF arm sustained the sUA response at Week 24 vs 30% from the placebo arm (*P*=0.06)
- There were no infusion reactions in the MMF group; however, 3 patients in the placebo group experienced infusion reactions (0% vs 30%)

Pegloticase and use of immunmodulation trends



Note: Immunomodulation/pegloticase co-therapy usage defined as: Any patient starting either methotrexate or azathioprine within 60 days of their first pegloticase infusion date, excluding immunotherapy usage more than 1 year before starting pegloticase

LaMoreaux B, et. al. Presented at: EULAR 2020 E-Congress; Jun 3-Sep 1, 2020. Virtual. Abstract 3OP0173.

Summary

- Gout is a chronic, progressive arthritis caused by hyperuricemia with associated chronic inflammation
- Total body urate burden extends beyond clinically and physically apparent tophi
- The NLRP3 inflammasome up-regulates IL-1 expression in gout and is the same mechanism in other autoinflammatory diseases such as the periodic fever syndromes
- NETs play a major role in gout, resulting in tophus formation and bone erosion in the absence of pain
- Our evolving understanding of the etiopathogenesis of gout may lead to new treatment possibilities, e.g. IL-1 inhibitors, NETosis, bone-strengthening agents

Summary continued

- Gout is an autoinflammatory disorder with common mechanisms of disease as other rheumatic diseases, like the periodic fever syndromes, rheumatoid arthritis, lupus, and osteoporosis
- Hence, treatment paradigms of gout should similarly change
  - earlier detection and diagnosis
  - greater embrace of treat-to-target approach
  - more aggressive treatment strategies
  - increased utilization of biologic therapies
  - goal of remission/functional cure of gout
- 2020 ACR Guidelines for Gout Management provide updates to direct clinical care
- Concomitant immunomodulation with pegloticase may increase response rates and tolerability

Thank you !