Update on the Management of Gout:2017

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Learning Objectives

- Understand the pathophysiology of monosodium urate crystal formation
- Understand correct prescribing of colchicine
- Become familiar with urate-lowering medications
- Recognize the difference between treatment guidelines published by American College of Physicians and American College or Rheumatology

Disclosures

- None relate to this presentation
- Consultant
  - Mallinckrodt
- Speaking
  - Pfizer
  - Novartis
  - Mallinckrodt
  - Celgene
- Clinical Trial Support
  - Mallinckrodt
  - GSK

CO-15

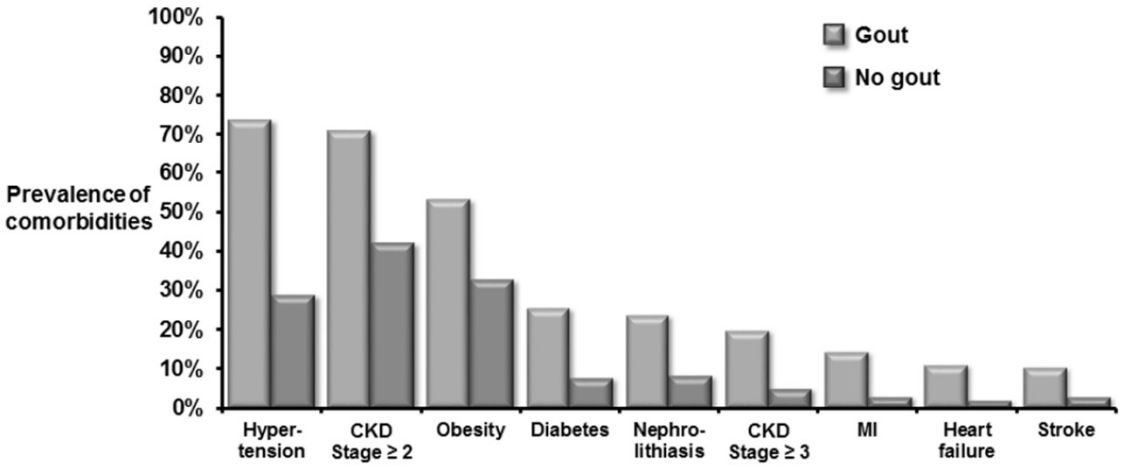
Gout is Urate Crystal Deposition Disease

- Affects ~8.3 million people in US[1]
- Results from elevated levels of urate in blood or hyperuricemia
  - Over-production (~10%)
  - Under-excretion (~90%)[2]

1. Zhu, 2011. 2. Vazquez-Mellado, 2007.

CO-22

Serious Comorbidities Associated with Gout

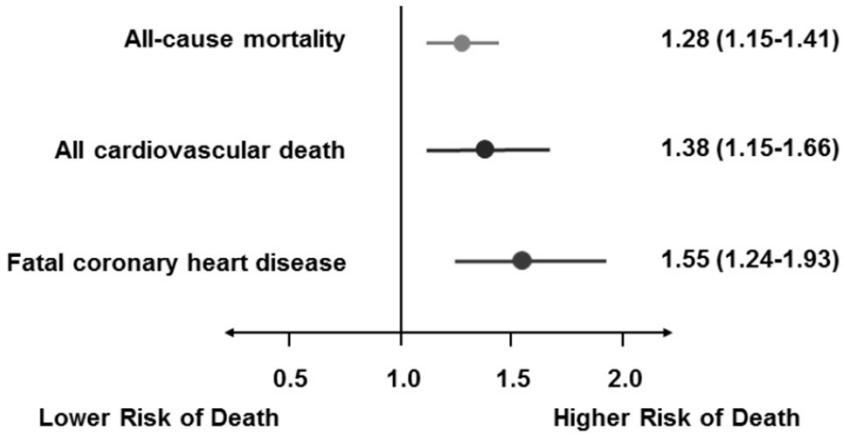


Zhu, 2012.

CO-23

Increased Risk of CV Death Associated with Gout

Multivariable Relative Risk (95% CI) of Death in Patients with Gout

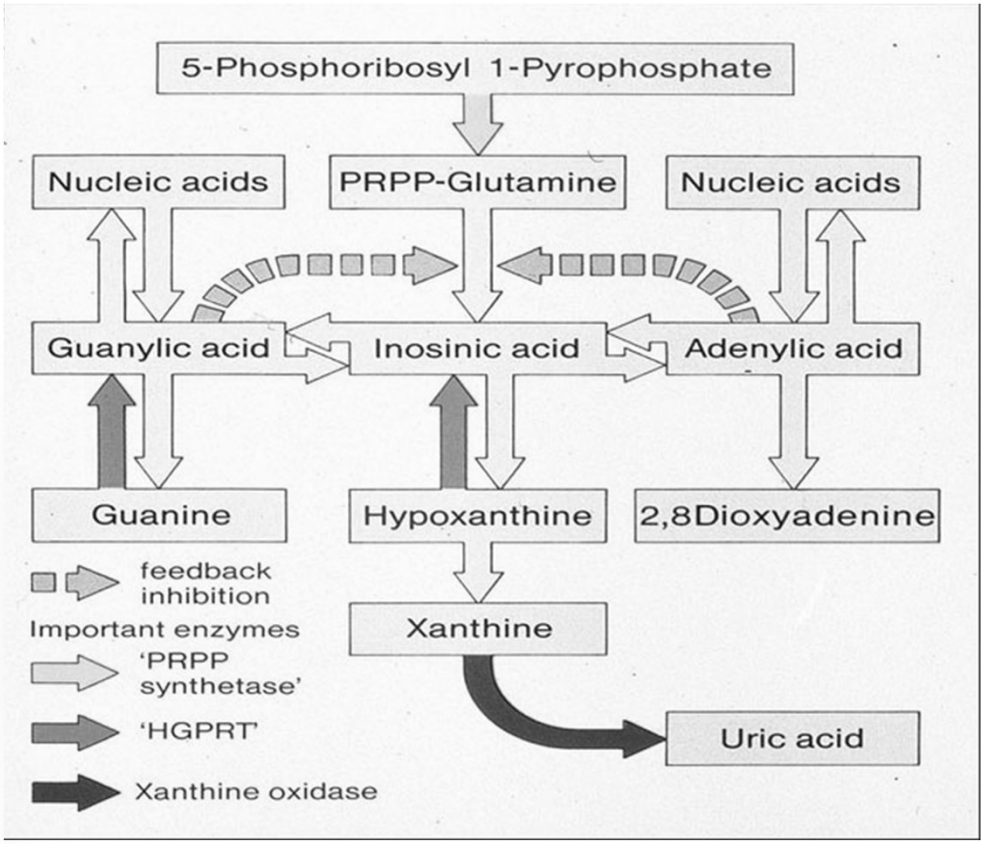


Choi, 2007.

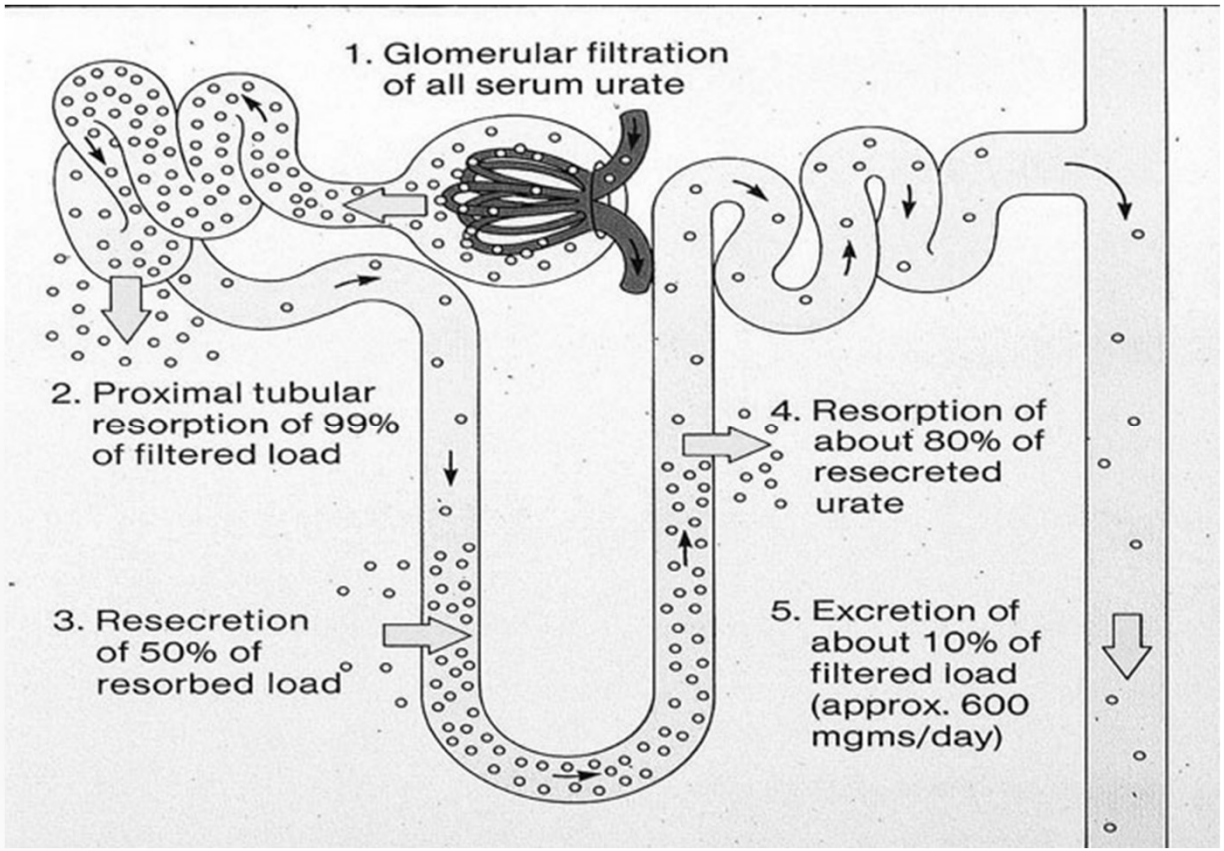
BRIEF review of the essentials

- Gout occurs when monosodium urate crystallizes under physiologic conditions, when its concentration exceeds its solubility (6.8 mg/dl)
  - Only 1 in 30 with hyperuricemia develop gout
- 90% of hyperuricemia is caused by UNDEREXCRETION
- Most patients with recurrent gout attacks will require medication to lower the serum UA

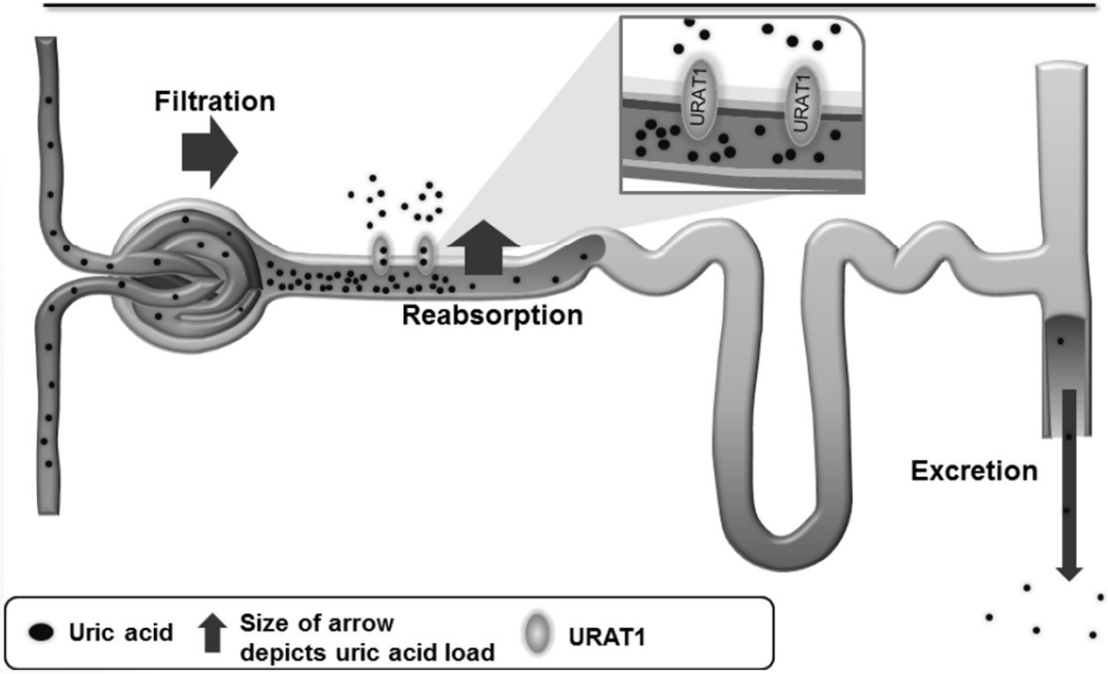
PURINE METABOLISM



RENAL HANDLING OF URATE



Normal Renal Handling of Uric Acid



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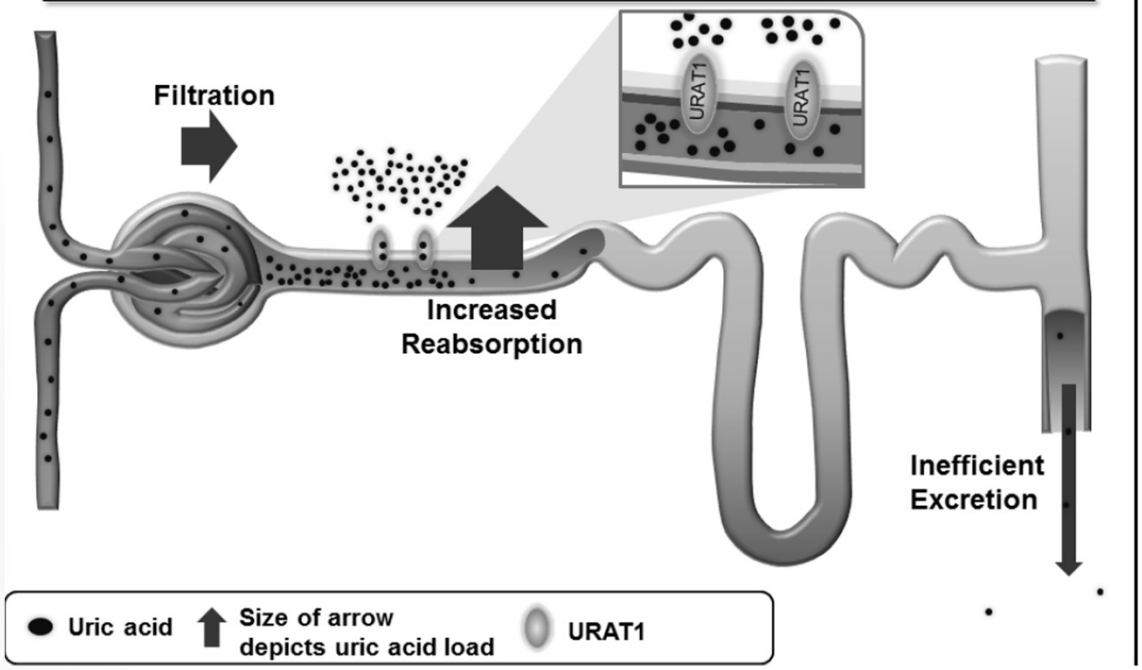
Inefficient Excretion of Uric Acid in Patients with Gout

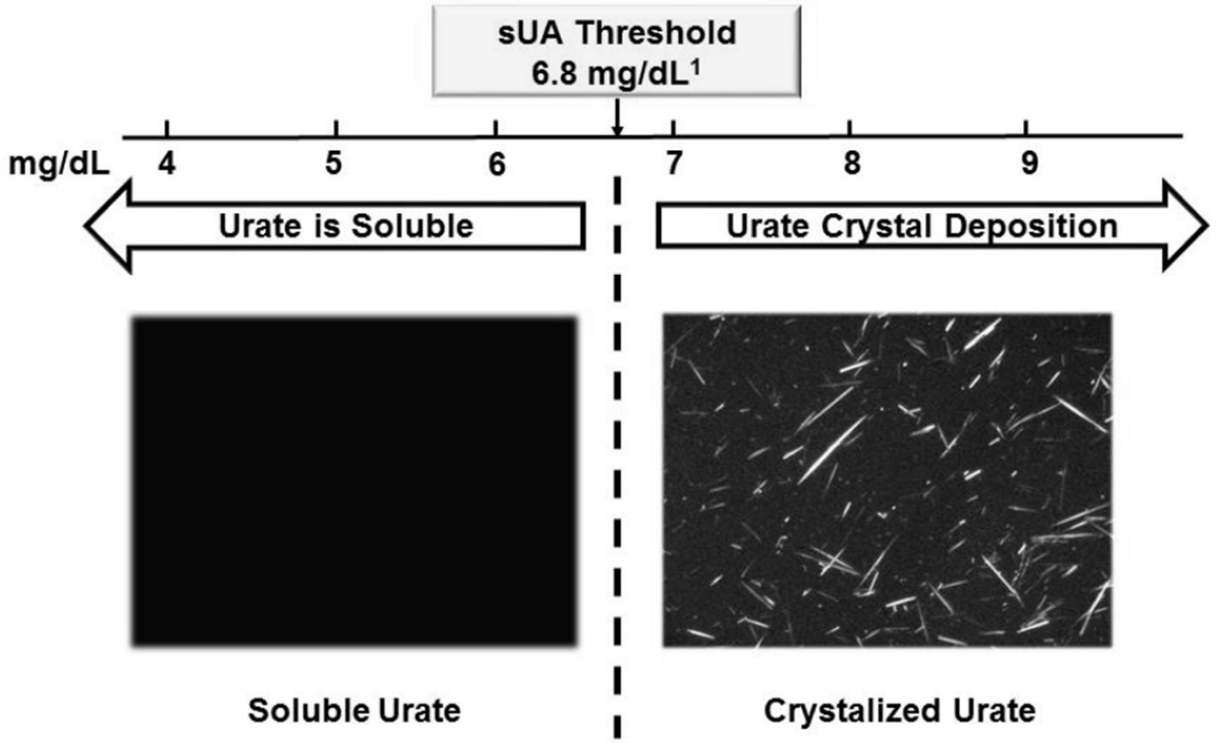


PATHOGENESIS OF URATE CRYSTAL DEPOSITION

- Limit of solubility of urate in serum is 6.8 mg/dl (WITHIN THE "NORMAL" range!)
  - Urate crystallizes as a monosodium salt in oversaturated joint tissues
  - At decreased temperature of periphery (e.g. feet), solubility is even less

CO-16

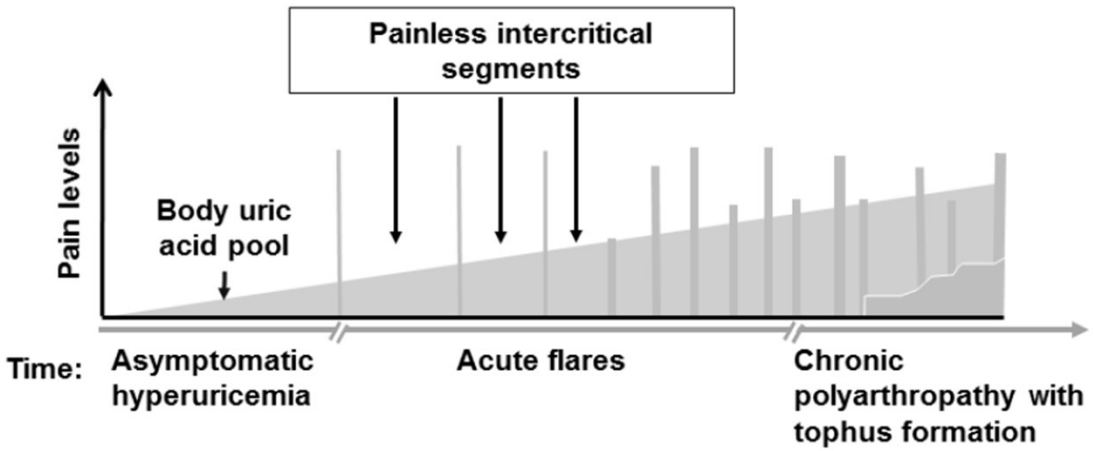
Solubility Threshold of Urate



1. Loeb, 1972.

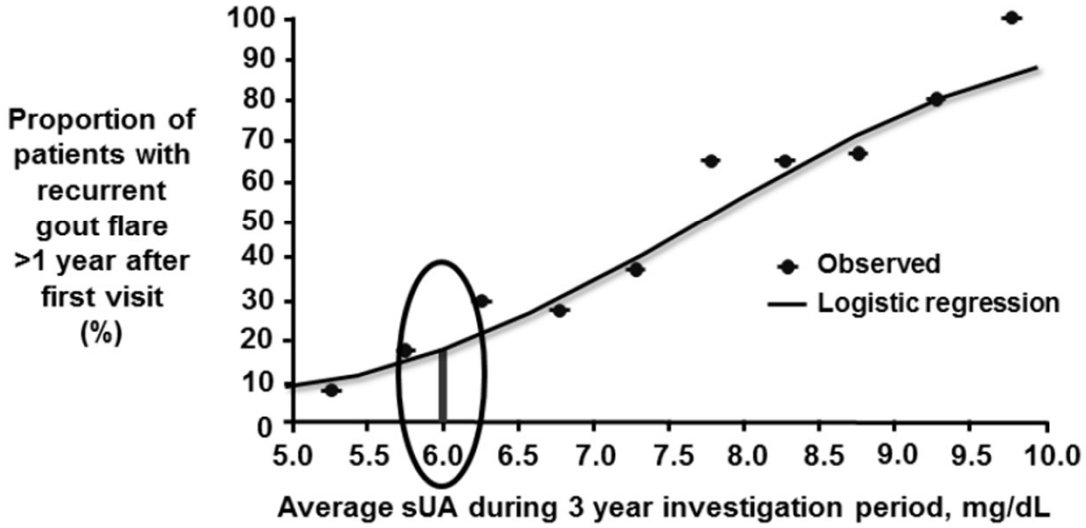
CO-18

Gout Develops and Progresses over Time as Uric Acid Load Increases



1. Doghramji, 2012.

Increase in Gout Flare Recurrence with Increasing sUA

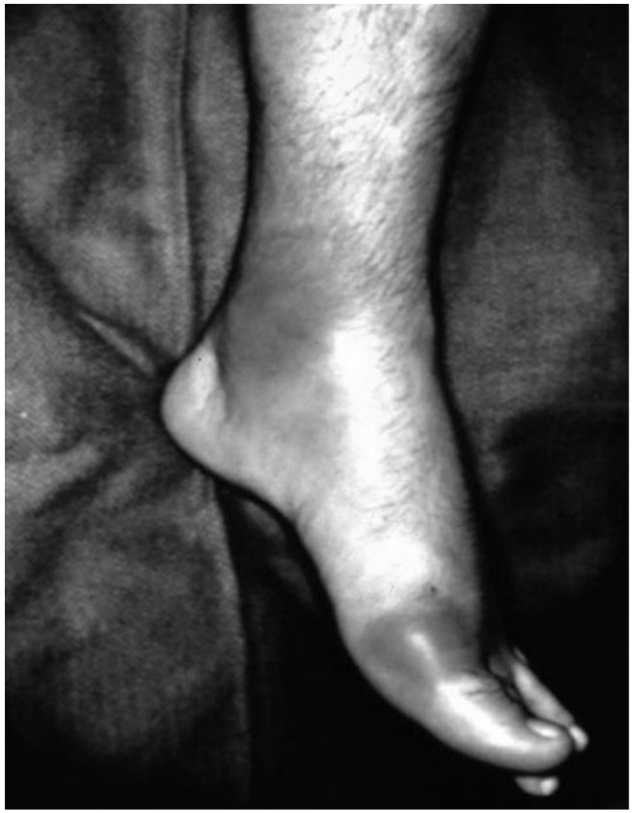


- 86% (71/81) of patients who had sUA <6.0 mg/dL did not experience acute flare during study period

Shoji, 2004.

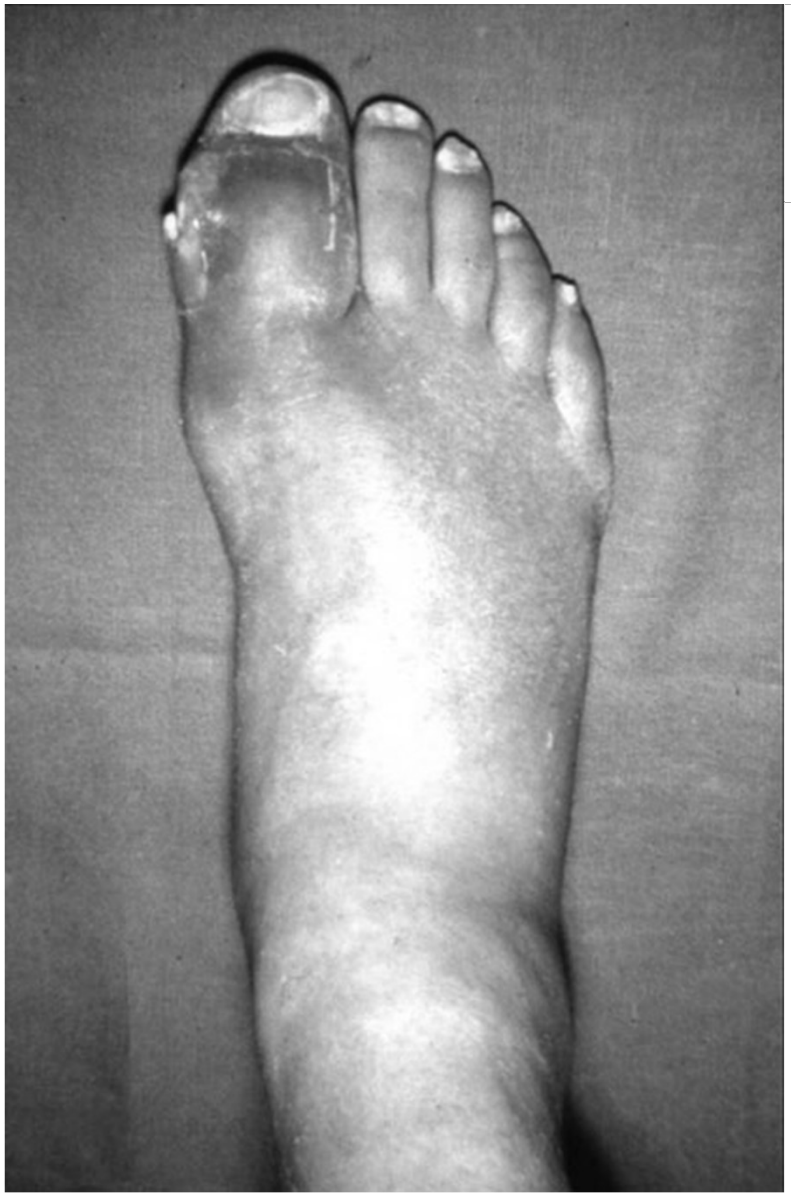
Acute Gouty Arthritis

ACUTE GOUT: PODAGRA

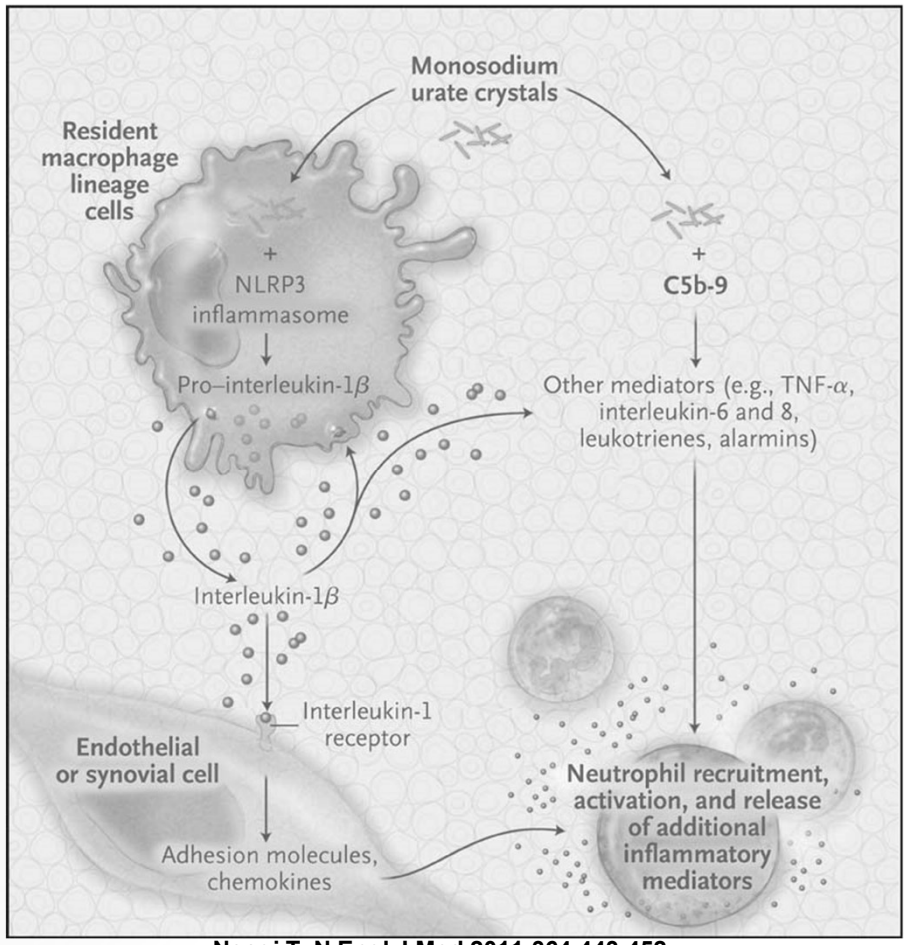


ACUTE GOUTY ARTHRITIS

- First MTP
- Desquamation from severe periarticular inflammation



Mechanisms of Inflammation in Gout.



Neogi T. N Engl J Med 2011;364:443-452

Pharmacologic Management Options for Acute Gout Attacks.

Table 1. **Pharmacologic Management Options for Acute Gout Attacks.**

Drug	Examples of Regimens from Randomized Clinical Trials	Alternative Regimens for Complete Attack Resolution*	Precautions
Nonsteroidal antiinflammatory drug†			Avoid in patients with renal or hepatic insufficiency, bleeding disorder, congestive heart failure, or allergy; associated with an increased risk of adverse thrombotic and gastrointestinal events; may be administered with a proton-pump inhibitor in patients at risk for gastrointestinal events.
Naproxen	500 mg orally twice daily for 5 days	375–500 mg orally twice daily for 3 days, then 250–375 mg orally twice daily for 4–7 days or until attack resolves	
Indomethacin	50 mg orally three times daily for 2 days, then 25 mg orally three times daily for 3 days	50 mg orally three times daily for 3 days, then 25 mg orally three times daily for 4–7 days or until attack resolves	
Colchicine	1.2 mg orally at first sign of gout flare, followed by 0.6 mg orally 1 hr later	Consider additional acute gout regimen to continue managing attack 12–24 hr after colchicine regimen (e.g., 0.6 mg of colchicine twice daily, a nonsteroidal antiinflammatory drug regimen, or an oral glucocorticoid regimen until attack resolves)	Avoid (or use lower dose) in older adults and those with renal insufficiency, hepatic dysfunction, or known gastrointestinal symptoms; adjust dose (and avoid in patients with renal or hepatic impairment) if used in conjunction with P-glycoprotein or CYP3A4 inhibitors (e.g., cyclosporine, clarithromycin, certain antiretroviral agents, certain antifungal agents, certain calcium-channel blockers, and grapefruit juice); avoid for gout-flare therapy in patients with renal or hepatic impairment who are already receiving colchicine prophylaxis; monitor for gastrointestinal symptoms, myotoxicity, and blood dyscrasias (details are available at www.fda.gov).
Oral glucocorticoids (prednisone or prednisolone)‡	Prednisolone, 30–35 mg daily for 5 days	Prednisone, 30–60 mg daily for 2 days (depending on severity of attack), then reduce by 5–10 mg every 2 days (depending on starting dose) in 10-day taper	Use caution in patients with hyperglycemia or congestive heart failure; may be used in patients with moderate-to-severe renal impairment.

* Longer durations of therapy may be necessary for patients with long-standing disease and severe flares.
† There are no published trials establishing the efficacy of celecoxib, the only selective cyclooxygenase-2 inhibitor available in the United States, for use in acute gout.
‡ Although there are insufficient data to recommend the use of intraarticular glucocorticoid injection, it may be a useful alternative for attacks that are limited to one or two joints and amenable to aspiration and in the absence of joint sepsis.

Neogi T. N Engl J Med 2011;364:443-452

The NEW ENGLAND JOURNAL of MEDICINE

“New” prescribing information on colchicine

Treatment of Acute Gouty Arthritis

- Colchicine is a plant alkaloid derived from the autumn crocus (Colchicum autumnale) First described by Greek surgeon Padanius Dioscorides around the year 60 CE
- Extracts in widespread use since early 1800
- Colchicine stops the microtubular formation of the inflammasome if given EARLY in the gout attack; not effective once the inflammasome has formed

Colcrys: Brand Name Colchicine

- FDA concerned that colchicine had never been formally approved for treatment of gout
- Also concerned about FATAL colchicine toxicity with standards doses
- *"Oral colchicine has been used for many years as an unapproved drug with no FDA-approved prescribing information, dosage recommendations, or drug interaction warnings"*
- Producers of colchicine were offered the opportunity to submit data for approval

DOSAGE AND ADMINISTRATION*

- **Gout Flares**: 1.2 mg (2 tablets) at the first sign of a gout flare followed by 0.6 mg (1 tablet) one hour later
- Higher doses have not been found to be more effective.
- The maximum recommended dose for treatment of gout flares is 1.8 mg over a 1 hour period.

- *package insert

DOSAGE AND ADMINISTRATION*

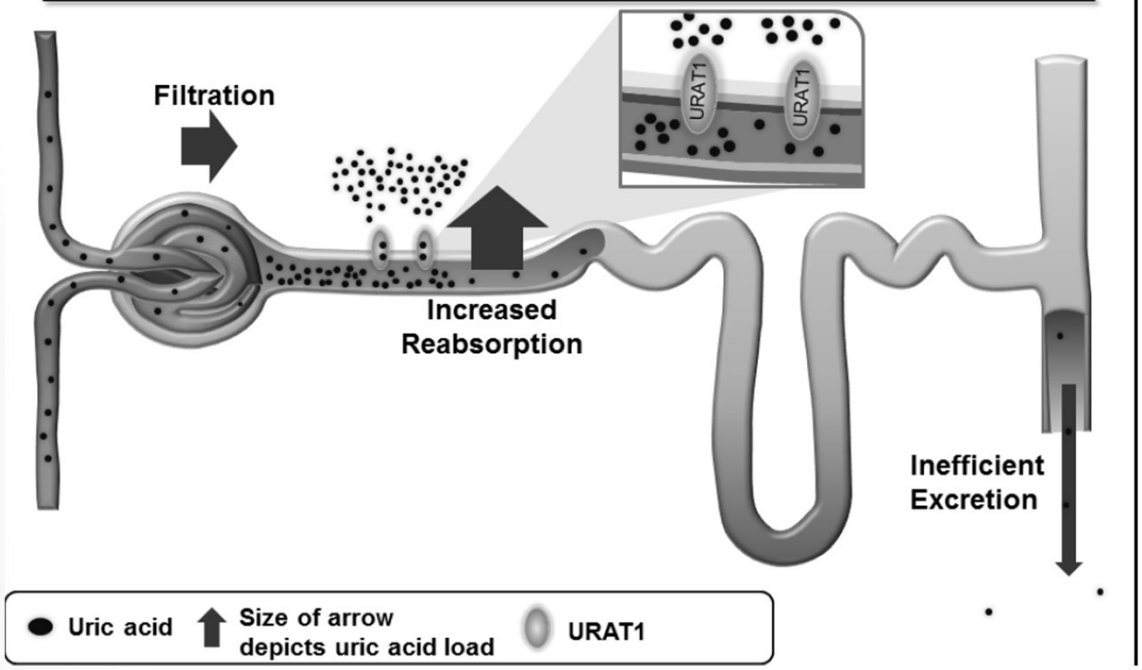
- In the presence of renal impairment, dosing for gout flares should be repeated no more than once every two weeks
- For patients undergoing dialysis, the total recommended dose for gout flares should be reduced to 0.6 mg (1 tablet) x 1 dose.
- For gout flares, a treatment course should be repeated no more than once every 2 weeks with no increase in dosage

- *package insert

Hyperuricemia

CO-95

Inefficient Excretion of Uric Acid in Patients with Gout



HYPERURICEMIA

- Underexcretion in 90%
  - Tubular secretion of urate decreased by
    - Thiazide diuretics (proximal tubule)
    - Salicylates (low dose)
    - Cyclosporine
      - Especially for cardiac transplantation
      - One in six patients with cyclosporine-induced hyperuricemia develop gout
      - Shorter asymptomatic period
    - Familial juvenile hyperuricemic nephropathy

Pharmacologic Options for Hyperuricemia Therapy in Gout.

Table 2. **Pharmacologic Options for Hyperuricemia Therapy in Gout.***

Drug	Example of Regimen	Considerations or Precautions
Urate-lowering therapy		Aim to maintain serum urate levels below 6 mg per deciliter, which requires regular monitoring and may require dose adjustments. Accompany the initiation of therapy with flare prophylaxis.
Xanthine oxidase inhibitor		Use in patients with urate overproduction or underexcretion. Avoid use (or monitor closely) in patients receiving azathioprine or 6-mercaptopurine because these drugs are metabolized by xanthine oxidase.
Allopurinol	Starting dose: 50–100 mg orally daily; increase dose every 2–4 wk to achieve serum urate target, with dose based on creatinine clearance; average daily dose, 300 mg, although many patients require higher doses	Use with caution in patients with renal insufficiency (based on creatinine clearance). The maximal dose may be as high as 800 mg daily, but there are limited data for doses above 300 mg daily. A mild rash occurs in approximately 2% of patients, and the risk is potentially increased by coadministration of ampicillin, amoxicillin, thiazide diuretics, or ACE inhibitors. Allopurinol hypersensitivity is rare, occurring in approximately 0.1% of patients, but can be fatal (rate of death, 20%). If the target serum urate level is not achieved, consider dose escalation beyond the level suggested by guidelines in patients with renal impairment (with close monitoring) or consider the use of an alternative therapy (e.g., febuxostat). Allopurinol can increase the anticoagulant effect of warfarin.
Febuxostat	Starting dose: 40 mg orally daily; increase to 80 mg orally daily after 2–4 wk to achieve serum urate target, if necessary†	Use as a second-line agent for patients who have contraindications or an inadequate response to allopurinol or uricosuric therapy. Although no dose adjustment is required for patients with mild-to-moderate renal or hepatic insufficiency, there are insufficient data for use in patients with a creatinine clearance of <30 ml per minute or severe hepatic impairment. Currently contraindicated for use with theophylline. Febuxostat has a higher cost than allopurinol.
Uricosuric agent (probenecid)‡	Starting dose: 250 mg orally daily; increase by 500 mg per mo to a maximal dose of 2–3 g per day (2 divided doses) in patients with normal renal function to achieve serum urate target	Avoid in patients with a history of nephrolithiasis and a creatinine clearance of <30 ml per minute. Adequate hydration is required to reduce risk of nephrolithiasis. The use of this drug can increase serum penicillin levels. Evaluate for renal uric acid excretion in patients with a family history of early onset of gout, onset of gout at <25 yr, or a history of nephrolithiasis, since this may identify patients with an overproduction of urate in whom uricosuric therapy should be avoided because of the risk of nephrolithiasis.
Uricase (pegloticase)	Intravenous infusion of 8 mg every 2 wk; requires premedication with antihistamines and glucocorticoids; start gout-flare prophylaxis ≥7 days before initiating treatment	Use for chronic gout in adults whose disease is refractory to conventional therapy (e.g., lack of normalization of serum urate, inadequate control of signs and symptoms with the use of a xanthine oxidase inhibitor at maximum medically appropriate dose, or other contraindication). There is a risk of infusion reactions (26%, vs. 5% in placebo group) even with premedication, particularly in patients without a therapeutic response (in whom serum urate levels increase to above 6 mg per deciliter, particularly on two consecutive occasions) or with antibodies against pegloticase. Anaphylaxis occurs in 5% of patients (vs. 0% in placebo group). No data are available regarding retreatment after stopping treatment for longer than 4 weeks. Do not use in patients with G6PD deficiency, and use caution in patients with congestive heart failure (insufficient safety data; some exacerbations in clinical trials). Cost is higher than for other therapies.
Flare prophylaxis during initiation of urate-lowering therapy		Aim to reduce the risk of flare during initial decrease in urate levels, presumably related to rapid mobilization of bodily urate stores. The duration of therapy is not well defined but treatment for at least 6 mo or until tophi resolve is recommended.
Colchicine	0.6 mg orally once or twice daily as tolerated	See Table 1 for precautions, particularly taking into account potential for increased toxic effects with prolonged therapy.
NSAID	Naproxen, 250 mg twice daily	See Table 1 for precautions, particularly taking into account potential for increased toxic effects with prolonged therapy. This drug has not been formally tested but has been used for prophylaxis in trials of urate-lowering therapies.

* ACE denotes angiotensin-converting enzyme, and NSAID nonsteroidal antiinflammatory drug.
† Febuxostat at a dose of 120 mg is available in Europe.
‡ Benzbromarone and sulfinpyrazone are available in a limited number of countries but not in the United States.

Neogi T. N Engl J Med 2011;364:443-452

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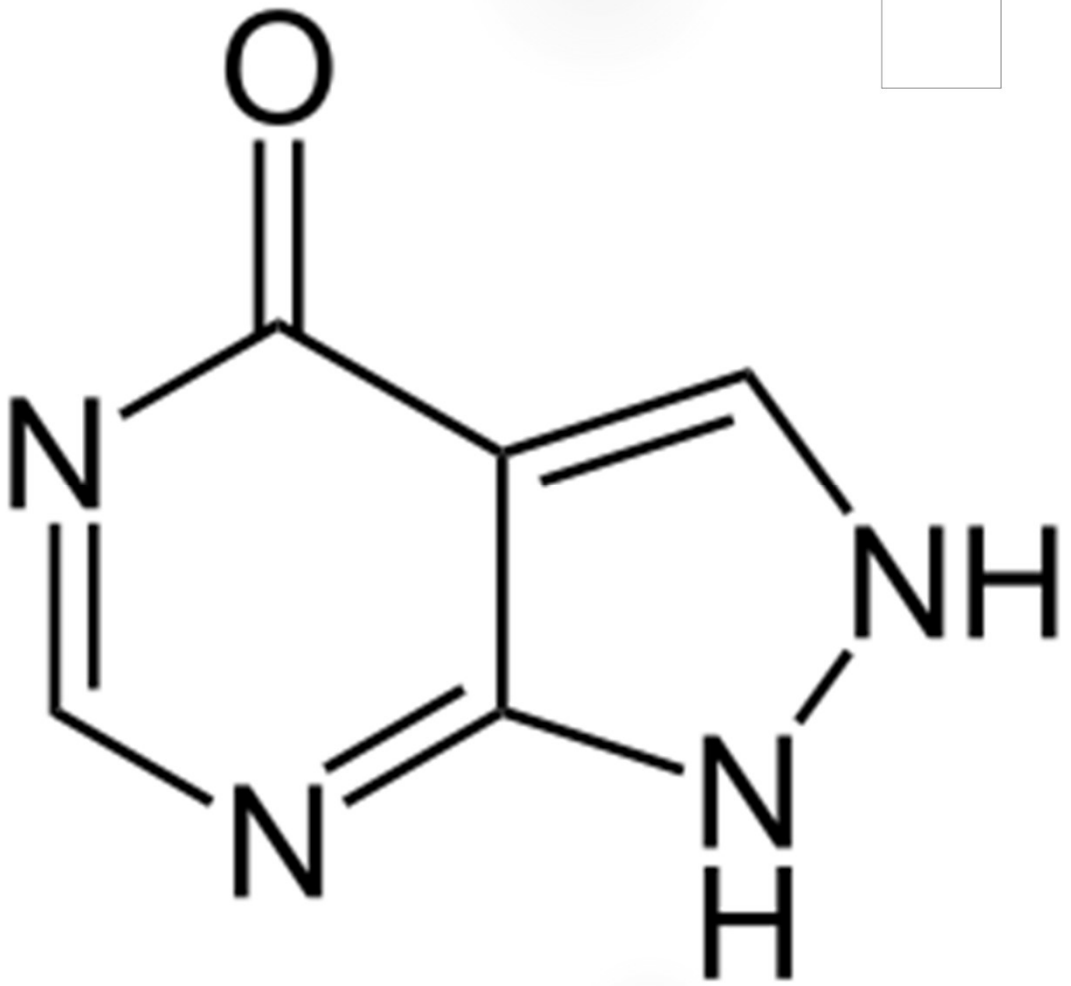
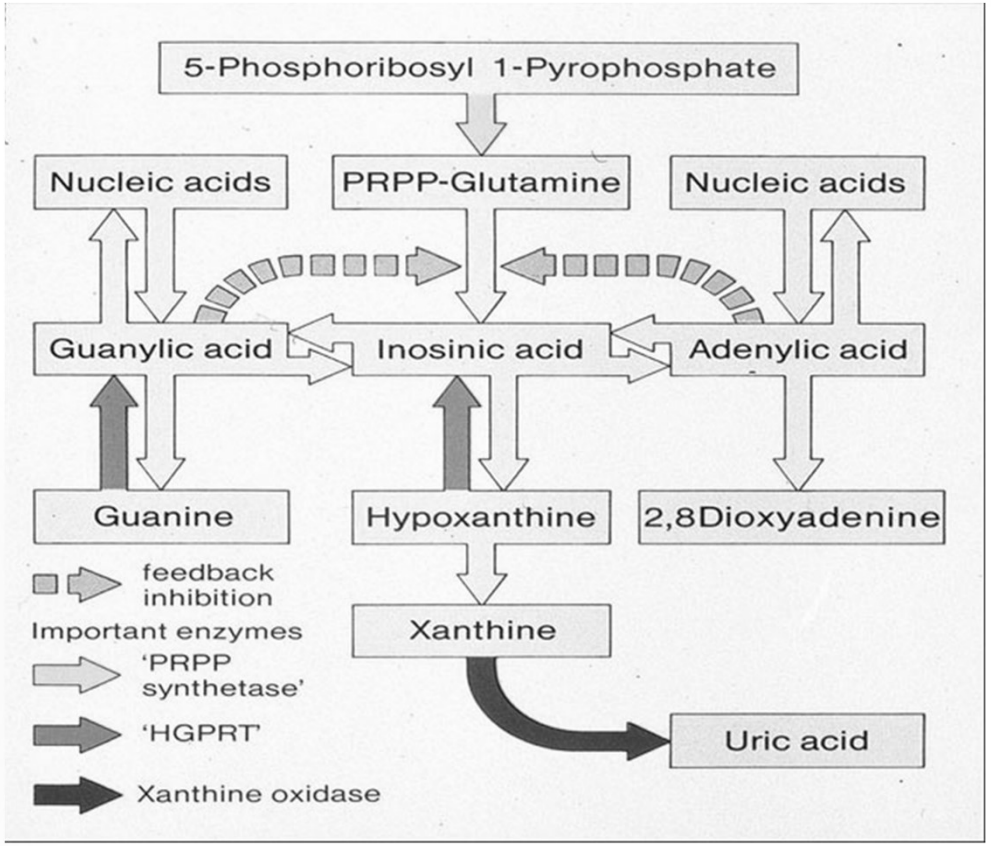
Allopurinol



PURINE METABOLISM



ALLOPURINOL

- Xanthine oxidase inhibitor
  - Blocks conversion of xanthine to uric acid
- Must use for
    - Overexcretors
    - Renal insufficiency
    - Nephrolithiasis
    - Tophi

The Controversy

- ACP guidelines and ACR guidelines do not agree
  - ACR guidelines recommended “Treat to Target” (T2T)
  - ACP guidelines recommended “Treat to Avoid Symptoms” (T2AS)

Correct Dose of Allopurinol…

- FDA approved up to 800 mg a day
- The goal of treatment is not a "normal" UA, but rather a concentration of UA at which urate will not crystallize
- …is the dose which results in a **serum UA of** <6

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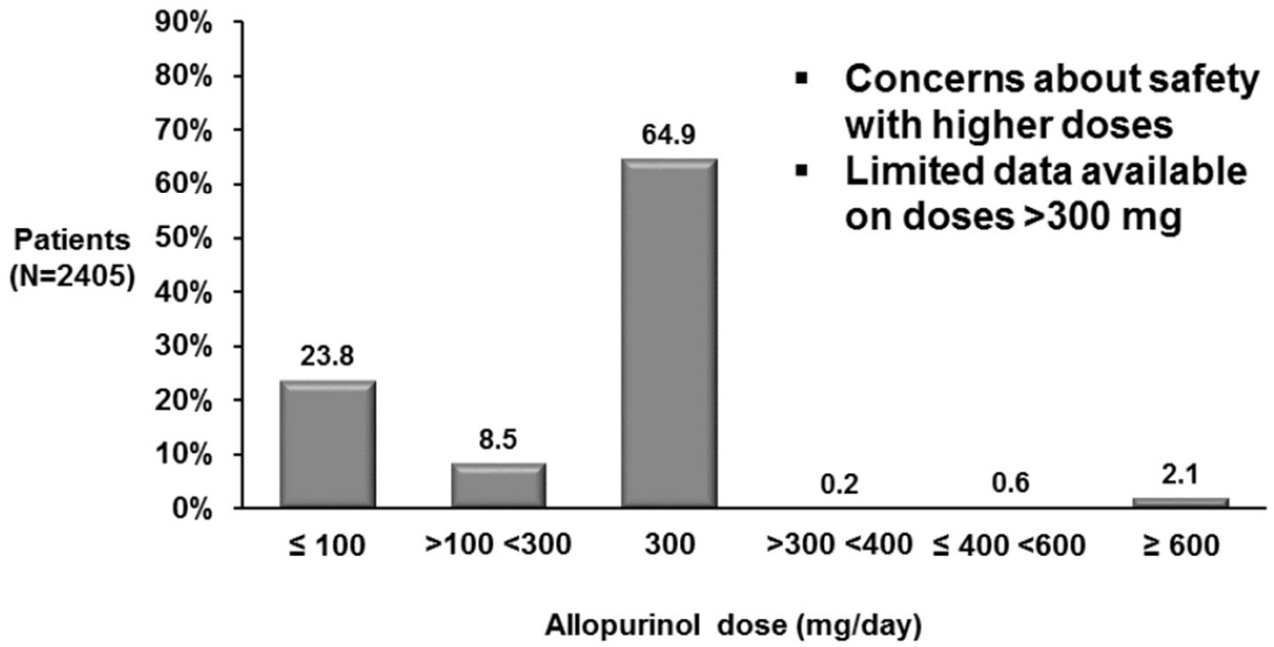
Allopurinol Doses >300 mg Rarely Prescribed



Sarawate, 2006.

Allopurinol

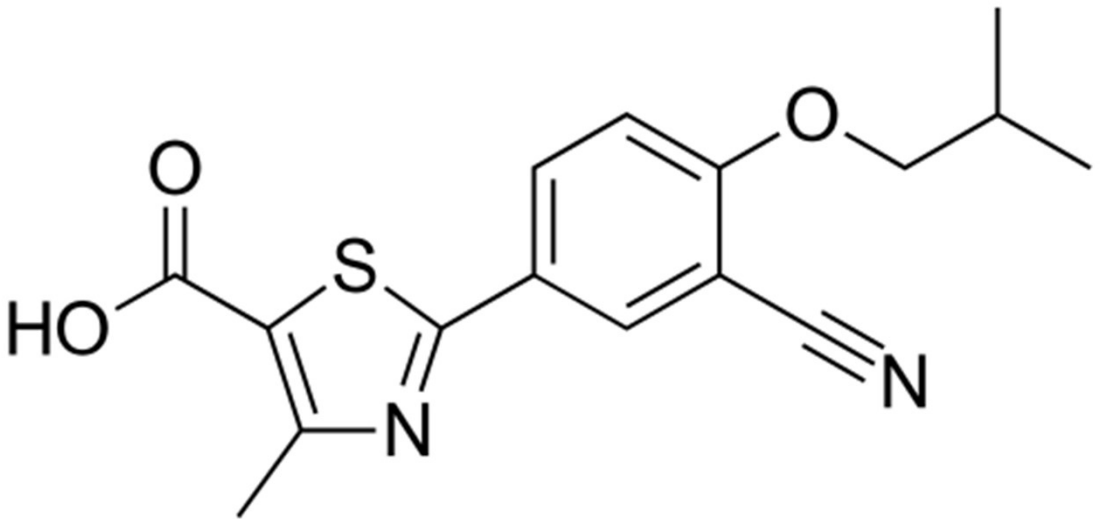
- Allopurinol hypersensitivity syndrome
  - Rare
  - Fever, rash, eosinophilia, hepatitis, renal failure
  - Can lead to death
  - More likely to occur in patients with CKD who are taking diuretics

Wortmann Curr Opin Rheumatol 2005; 17: 319-324.

Allopurinol Hypersensitivity Syndrome and HLA*B58:01

- HLA B*58:01
- Associated with Severe Cutaneous Adverse Reactions (SCAR), such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
- Individuals of Koreans, Han Chinese, and Thai descent
- This test is commercially available (Quest, Lab Corp)

Febuxostat



Febuxostat

- Chemically distinct from allopurinol
- Tolerated in patients sensitive to allopurinol
- Metabolized in the liver so dose adjustment not needed for CR CL >30 (no data for CR CL <30)

Febuxostat (continued)

- In a 4-week randomized, placebo-controlled study, 76% of gout patients receiving 80 mg daily …achieved serum uric acid levels <6.0, compared with 0% of those on placebo.

Becker *et al* Arthritis Rheum 2005; 52:916-923.

- Colchicine prophylaxis is needed during initiation of therapy

Febuxostat

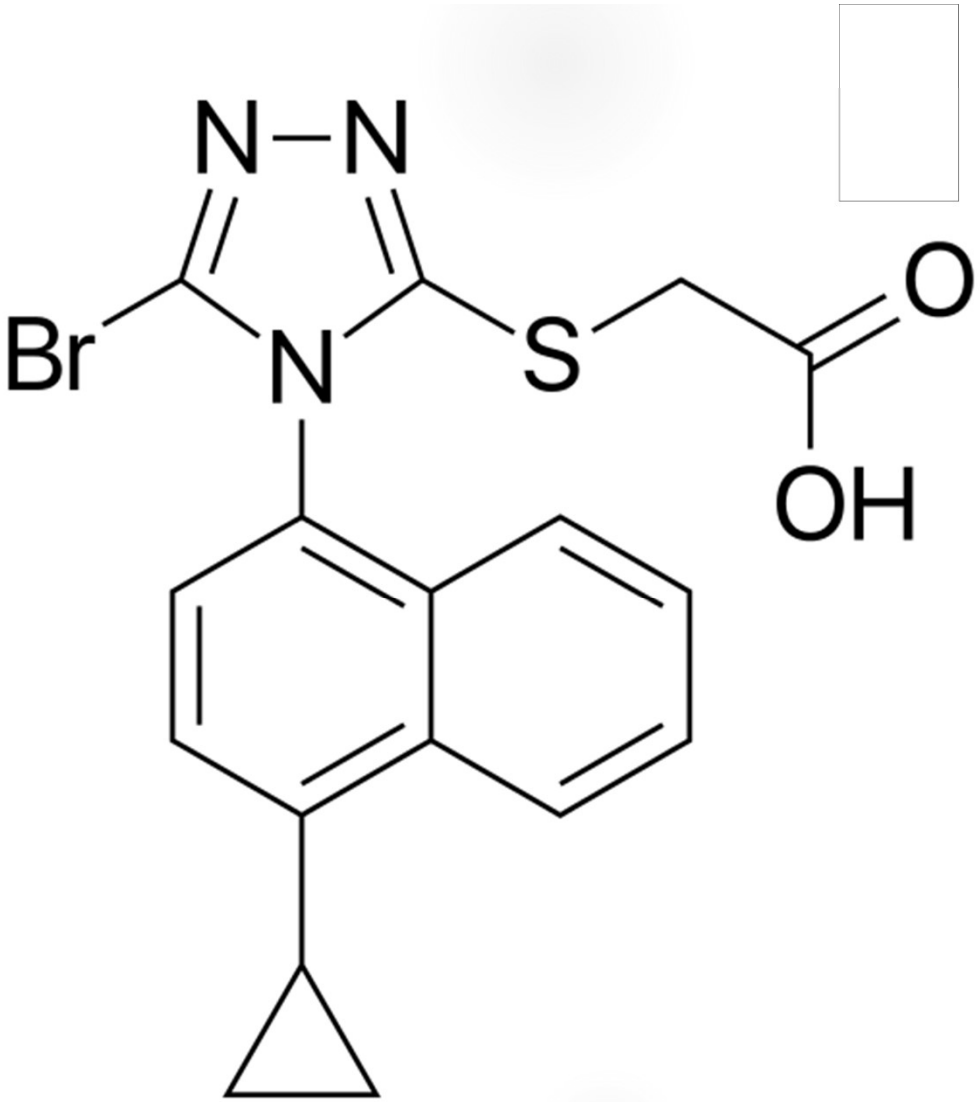
- Febuxostat 80 mg daily dosing shown to be more effective at achieving serum UA <6 than allopurinol 300 mg daily in a 52 week study in the U.S. and Canada

Becker *et al* N Engl J Med 2005; 353: 2450-2461.

Dosing of Febuxostat (Uloric)

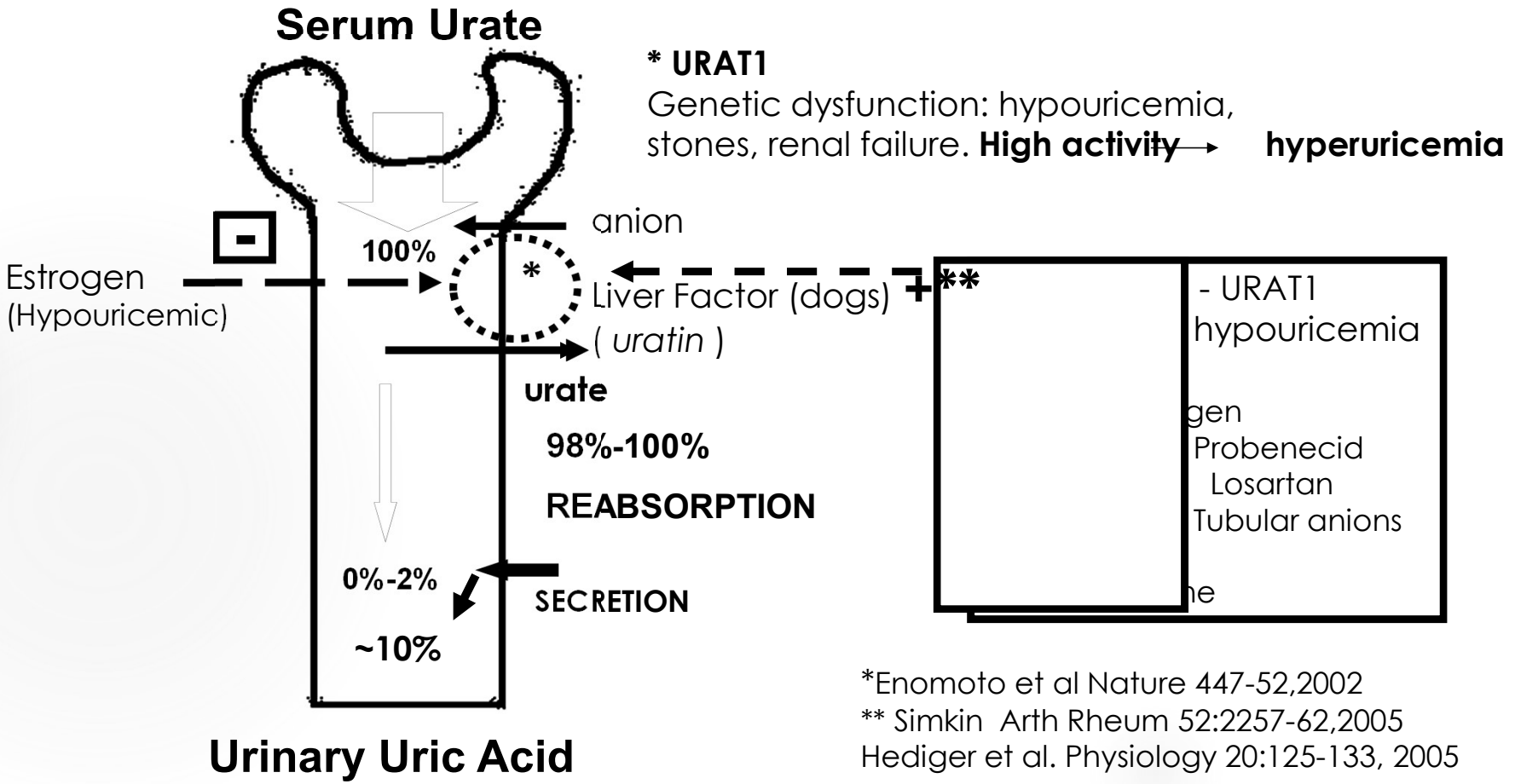
- Start at 40 mg daily
- Increase to 80 mg daily if serum UA is >6mg/dl after 2 weeks
- No data available
  - Doses > 80 mg/day
  - Use when Cr Cl < 30

Lesinurad



Renal Reabsorption of Uric Acid

URAT 1 (SLC22A12) Controls Serum Urate Level



*Enomoto et al Nature 447-52,2002
** Simkin Arth Rheum 52:2257-62,2005
Hediger et al. Physiology 20:125-133, 2005

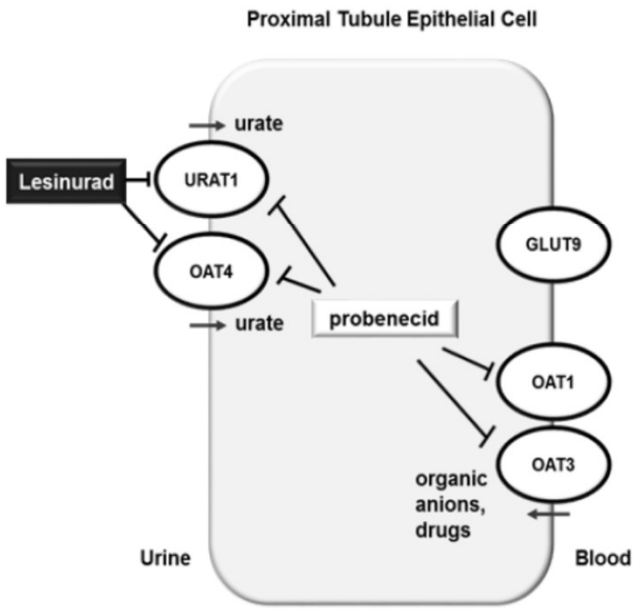
URAT1
RENAL URATE TRANSPORTER

- Anion exchanger
- In human proximal tubule cells (& smooth muscle)
- Oriented to reabsorb uric acid from tubule
- Genetic absence → uricosuria, hypouricemia, stones
- Inhibition → uricosuria, hypouricemia
  - Probenecid
  - Losartan
  - Benzbromarone
- Expression higher in male mice
  - Estrogen reduces synthesis

Reviewed in: Hediger et al. Physiology 20:125-133, 2005

Lesinurad is Novel, Oral Urate Lowering Therapy for Uncontrolled Gout

- Only uric acid transporter 1 (URAT1) inhibitor in 60 yrs
  - URAT1 inhibition increases uric acid excretion, lowers sUA
- First selective uric acid reabsorption inhibitor
  - Inhibits URAT1 and organic anion transporter OAT4
  - Does not inhibit OAT1 and OAT3



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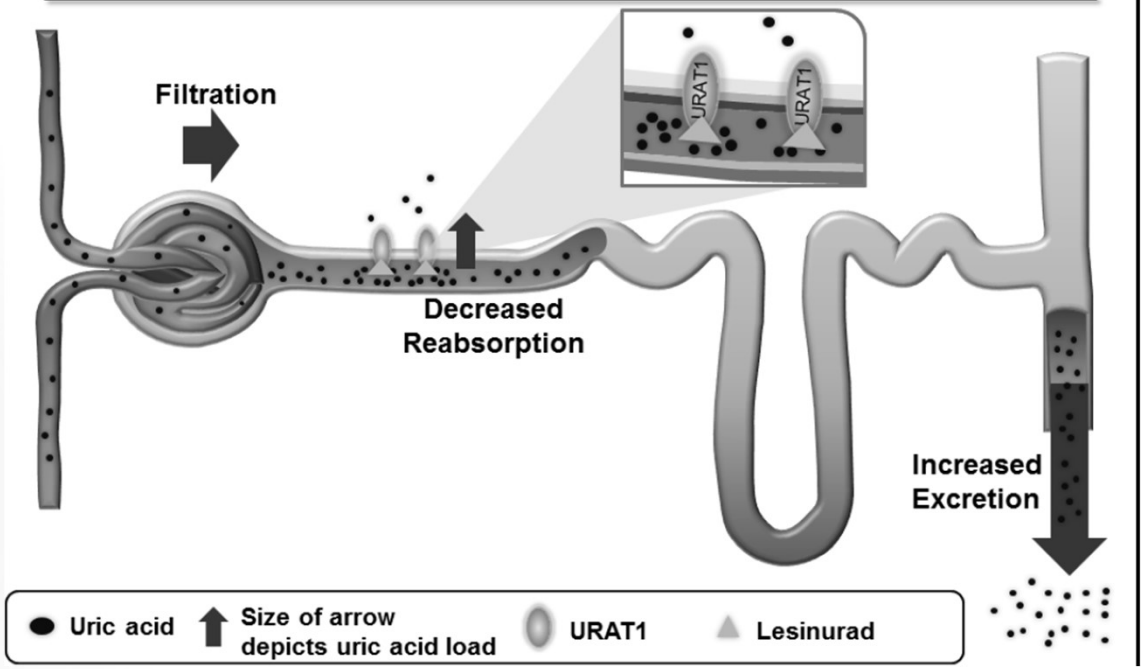
Lesinurad Increases Urinary Uric Acid Excretion



Lesinurad

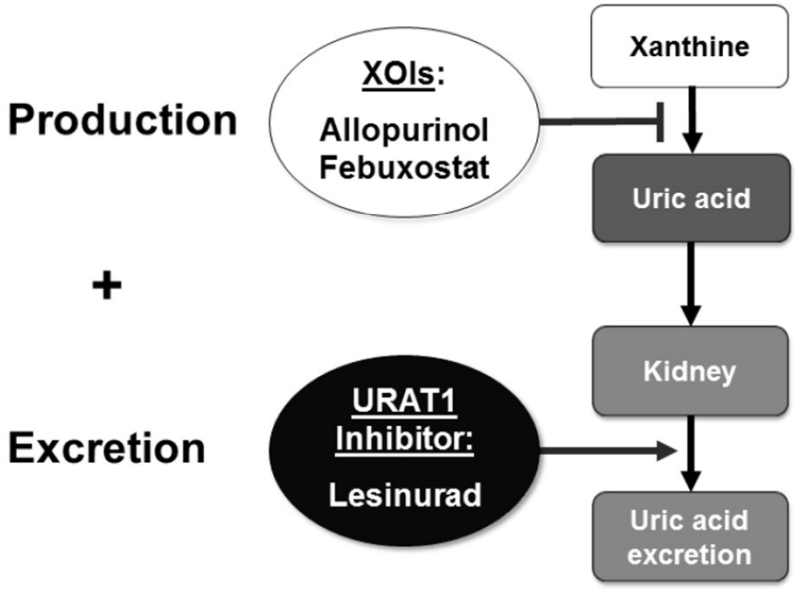
- Lesinurad is a uricosuric (selective uric acid reabsorption inhibitor) which was FDA approved in December 2015 for use at a dose of 200mg PO daily, in combination with a xanthine oxidase inhibitor (XOI)
- **Abstracts 206-209**: Lesinurad 12 month extension of several 12 month studies
  - Lesinurad 200 mg plus XOI and XOI alone had the comparable rates of AEs and renal AEs (kidney stones, rising creatinine); this did not change in the extension studies.
  - Adverse event rates were higher with lesinurad 400 mg daily plus XOI (c/w the other 2 groups), but this dose is not FDA approved.
  - Efficacy of XOI plus lesinurad 200 or 400mg persisted in the extension studies.

Lesinurad

- For patients on lesinurad 200mg or 400 mg daily in addition to a XOA in the extension trials
  - Tophi continued to shrink and resolve
  - Flares became increasingly rare
- **Conclusion:** The safety of lesinurad 200 mg po daily did not change over 2 years and the efficacy persisted.

CO-10

Dual Mechanism Approach: Lesinurad in Combination with XO Inhibitor



Lesinurad

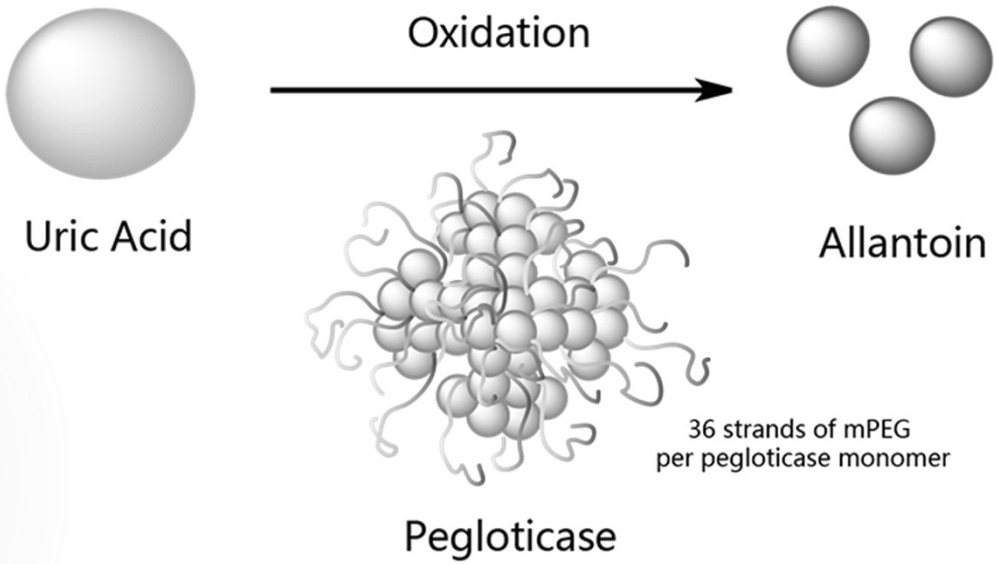
- #206 Terkeltaub R, Malamet R, Bos K, Li J, Goldfarb D, Pillinger M, Jalal D, Hu J, Saag K. Renal Safety of Lesinurad: A Pooled Analysis of Phase III and Extension Studies [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10). http://acrabstracts.org/abstract/renal-safety-of-lesinurad-a-pooled-analysis-of-phase-iii-and-extension-studies/.
- #207 Becker MA, Keenan RT, Khanna P, Malamet R, Bos K, Li J, Hu J, White W. Integrated Safety of Lesinurad, a Novel Uric Acid Reabsorption Inhibitor for the Treatment of Gout [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10). http://acrabstracts.org/abstract/integrated-safety-of-lesinurad-a-novel-uric-acid-reabsorption-inhibitor-for-the-treatment-of-gout/
- #208 Saag K, Becker MA, Storgard C, Fung M, Hu J, Bardin T. Examination of Serum Uric Acid (sUA) Lowering and Safety with Extended Lesinurad + Allopurinol Treatment in Subjects with Gout [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10). http://acrabstracts.org/abstract/examination-of-serum-uric-acid-sua-lowering-and-safety-with-extended-lesinurad-allopurinol-treatment-in-subjects-with-gout/.
- #209 Bardin T, Dalbeth N, Terkeltaub R, Storgard C, Fung M, Hu J, Perez-Ruiz F. Clinical Response of Tophus and Flares to Extended Use of Lesinurad in Combination with a Xanthine Oxidase Inhibitor in Patients with Gout [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10). http://acrabstracts.org/abstract/clinical-response-of-tophus-and-flares-to-extended-use-of-lesinurad-in-combination-with-a-xanthine-oxidase-inhibitor-in-patients-with-gout/.

PARADOX OF TREATMENT

- Rapid reduction urate levels can precipitate acute attack
  - Destabilization of microtophi in the gouty synovium, releasing urate crystals into synovial fluid
  - PMNs are more efficient in phagocytosis of crystals at lower urate concentrations
- Prophylactic colchicine or NSAIDs useful during the first few months of treatment

DO NOT STOP A URATE LOWERING DRUG DURING AN ACUTE ATTACKOF GOUT!!

Pegloticase



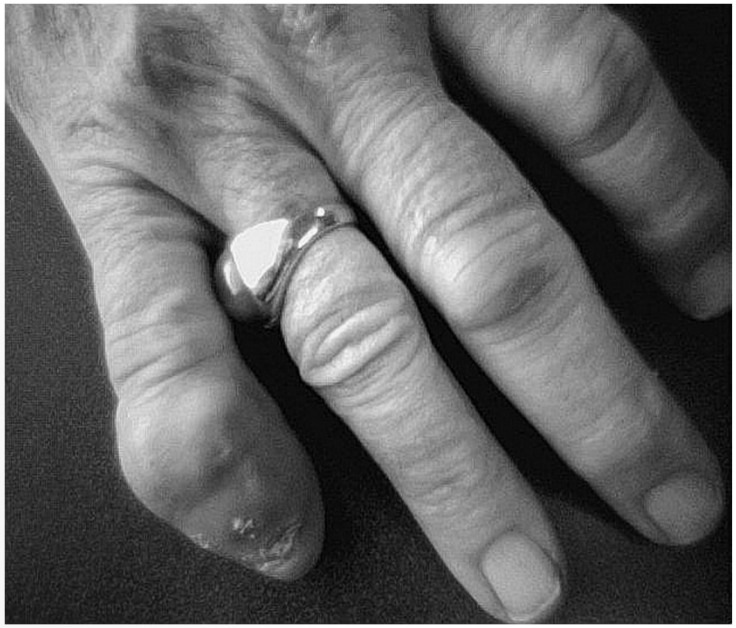
Uricase

- Uricase is an enzyme found in most non-primate mammals that converts relatively insoluble uric acid to allantoin, which is more soluble.
  - Foreign protein which can cause hypersensitivity reactions, including anaphylaxis, with repeated exposure
  - Can cause hemolysis and methemoglobinemia in G6PD deficiency

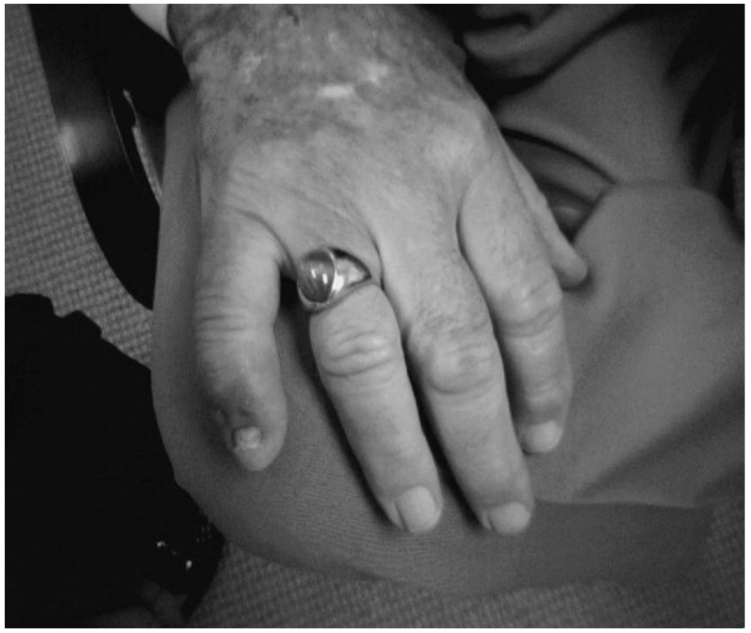
Krystexxa (pegloticase) administration

- 8 mg IV over 2 hours every 2 weeks
- Monitor serum uric acid levels before administration
  - D/C treatment if 2 UA levels > 6 mg/dl
  - Rising UA levels suggests antibody formation to medication
- Pre-medicate with antihistamines and corticosteroids
- Be prepared to manage anaphylaxis

Pegylated Uricase Therapy for Tophacious Gout



May, Pretreatment



July, 2 months post-treatment

Indications for Urate Lowering Medications

- Frequent and disabling attacks of gout
- Clinical or radiographic signs of chronic gouty joint disease
- Presence of tophaceous deposits
- Gout with renal insufficiency
- Recurrent nephrolithiasis
- Serum urate levels persistently >13 mg/dl in men or >10 mg/dl in women
- Urinary uric acid excretion >1100 mg/day
- Impending cytotoxic chemotherapy or XRT for leukemia or lymphoma

Adapted from Up to Date.

ACP Guidelines

- Annals of Internal Medicine November 1, 2016
- Standard literature review
  - Agency for Healthcare Research and Quality (AHRQ)-funded
  - ACP-directed
  - Geared guidelines to primary care providers (PCPs)
    - Excluded meds that PCPs are unlikely to prescribe, *e.g.* IL-1 inhibitors and pegloticase
    - Included febuxostat studies

ACP Guidelines

- ACP Guidelines for Management of Hyperuricemia in the Gout Patient
- ***Recommended treating to avoid symptoms [not to a particular serum uric acid (sUA) level] and therefore did not recommend monitoring sUA levels.***

"Management of Gout: A Systematic Review in Support of an ACP Clincial Practice Guideline"

- …"the *hypothesis* that lower serum urate levels are causally associated with a lower rate of acute gout attacks."
- "..no direct evidence supports or refutes the values of such monitoring" (referring to monitoring the serum urate levels in the context of administering ULT)
- "The evidence base for use of serum urate level as a target value for treatment is limited by the lack of any trial that has based treatment decision on different specific targets (such as a target of 7.0 vs 6.0 mg/dl) or any target as opposed to treating symptoms…The value of such a strategy has yet to be proved"
- "Thus, despite the strong biologic appeal of such a strategy and its advocacy by major specialty society guidelines*, we judged the strength of evidence for monitoring to be low"
- *American College of Rheumatology, European League Against Rheumatism, British Society for Rheumatology and British Health Professionals in Rheumatolgy Standards
- Ann Intern Med. 2017;166:37-51. doi:10:10.7326/M16-0461

The Controversy

- ACP guidelines do not agree with the ACR guidelines
  - ACR guidelines recommended “Treat to Target” (T2T)
  - ACP guidelines recommended “Treat to Avoid Symptoms” (T2AS)

"To Treat or Not to Treat (to Target) in Gout

- "Hyperuricemia is...the main pathophysiologic culprit that causes flares, tophi, and joint damage; therefore, management of hperuricemia is a key tenet of disease control"
- "When patients never receive ULT or receive inappropriately low doses, ongoing urate deposition occurs, leading to progression of tophaceous deposits, further joint damage, and functional limitations"
- "…for patients who start allopurinol therapy without a hypersensitivity reaction in the first 180 days or so, the likelihood of developing a reaction later is exceedingly low"

- Ann Intern Med. 2017:166:71-72. doi:10.7326/M16-2401

Disclosures

- None relate to this presentation
- Consultant
  - Mallinckrodt
- Speaking
  - Pfizer
  - Novartis
  - Mallinckrodt
  - Celgene
- Clinical Trial Support
  - Mallinckrodt
  - GSK

CO-15

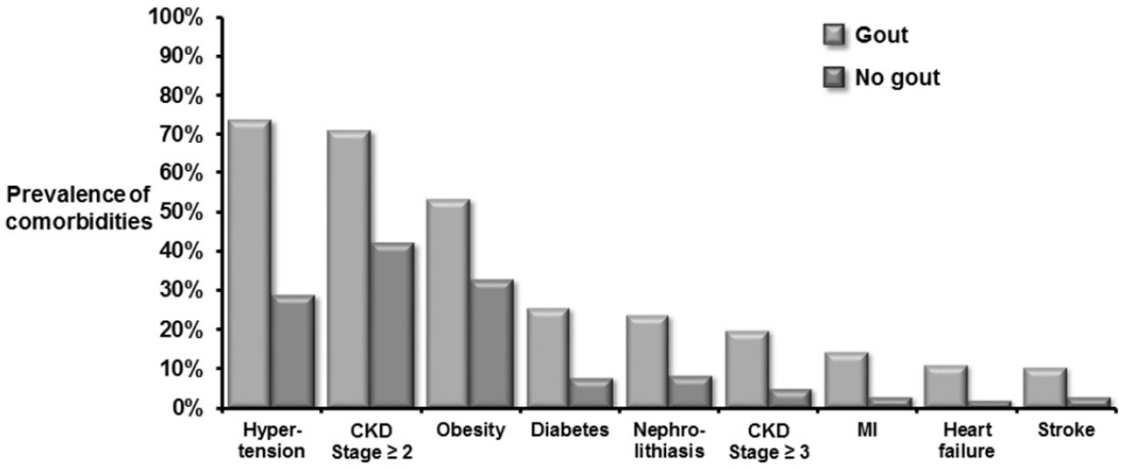
Gout is Urate Crystal Deposition Disease

- Affects ~8.3 million people in US[1]
- Results from elevated levels of urate in blood or hyperuricemia
  - Over-production (~10%)
  - Under-excretion (~90%)[2]

1. Zhu, 2011. 2. Vazquez-Mellado, 2007.

CO-22

Serious Comorbidities Associated with Gout

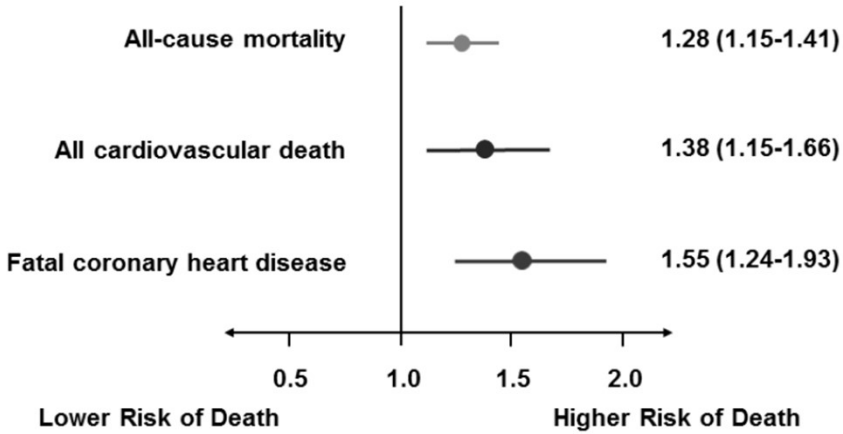


Zhu, 2012.

CO-23

Increased Risk of CV Death Associated with Gout

Multivariable Relative Risk (95% CI) of Death in Patients with Gout

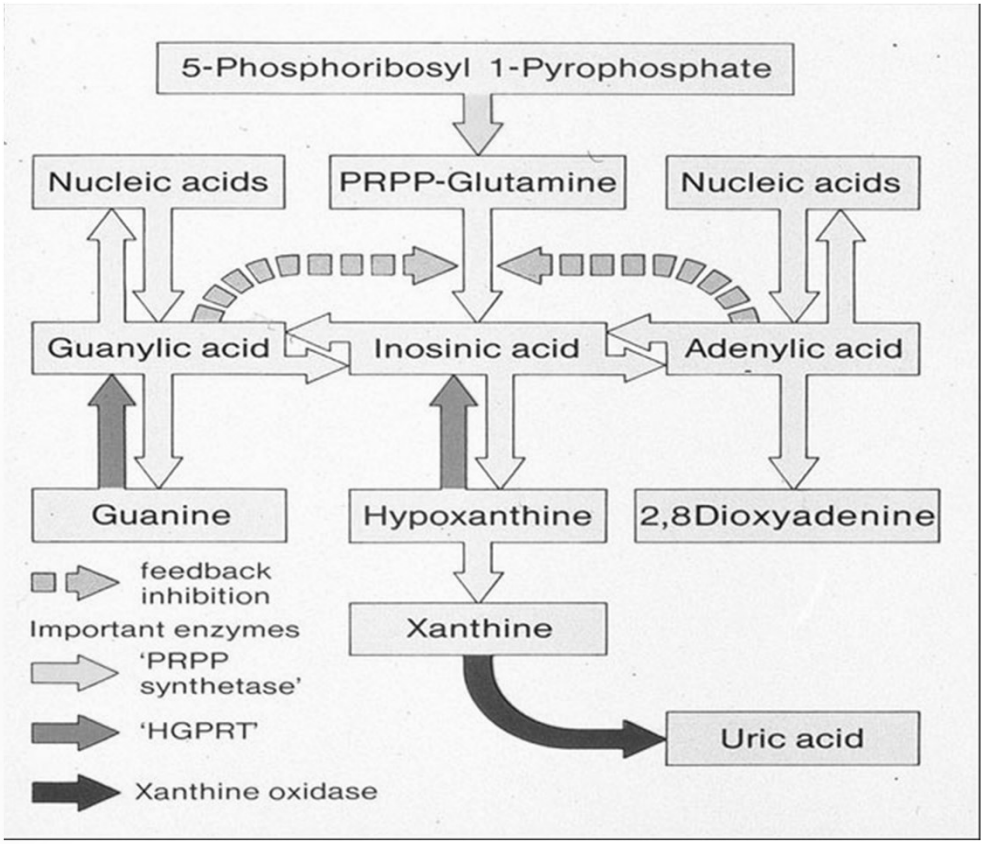


Choi, 2007.

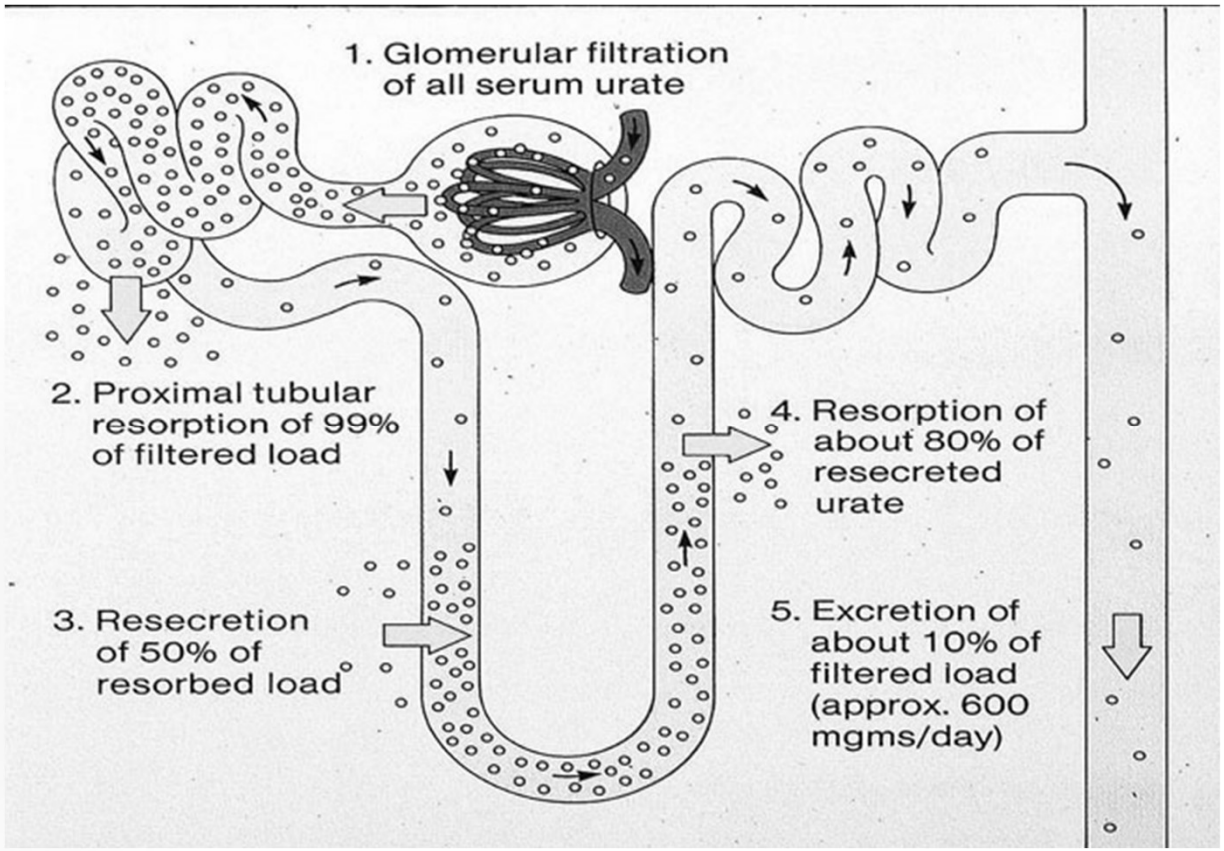
BRIEF review of the essentials

- Gout occurs when monosodium urate crystallizes under physiologic conditions, when its concentration exceeds its solubility (6.8 mg/dl)
  - Only 1 in 30 with hyperuricemia develop gout
- 90% of hyperuricemia is caused by UNDEREXCRETION
- Most patients with recurrent gout attacks will require medication to lower the serum UA

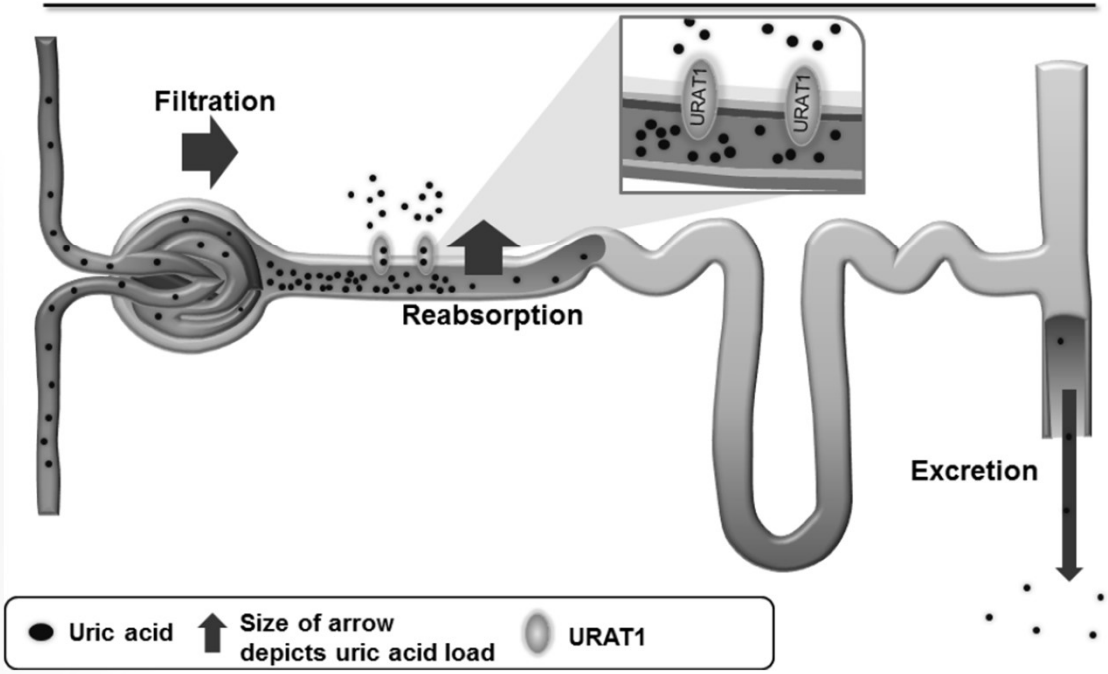
PURINE METABOLISM



RENAL HANDLING OF URATE

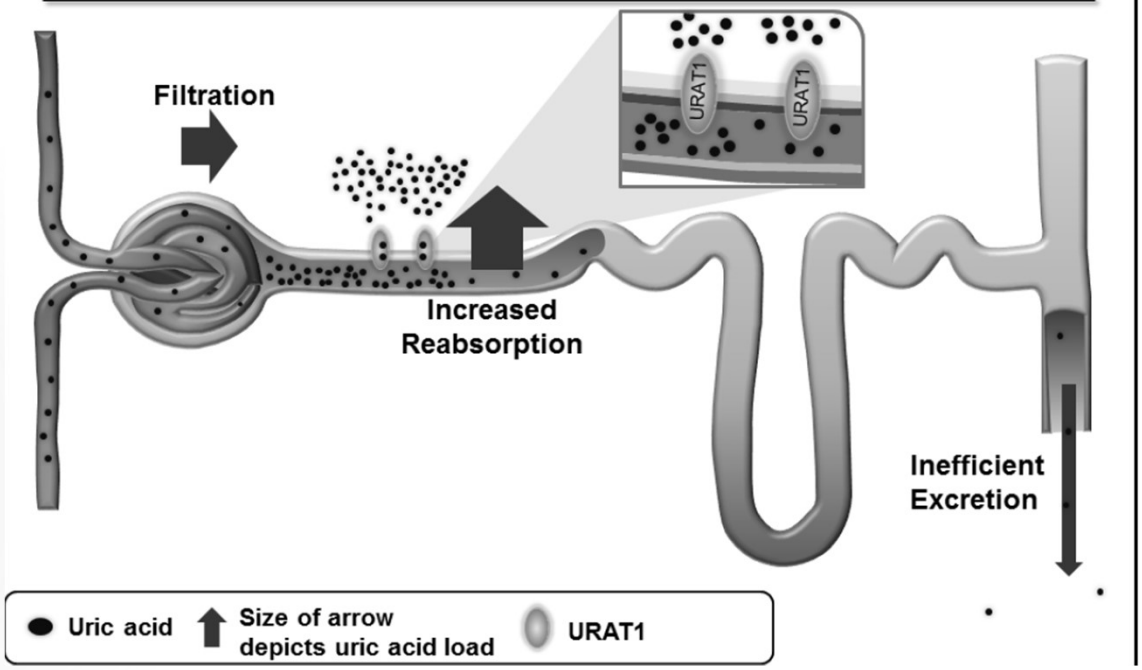


Normal Renal Handling of Uric Acid



CO-95

Inefficient Excretion of Uric Acid in Patients with Gout

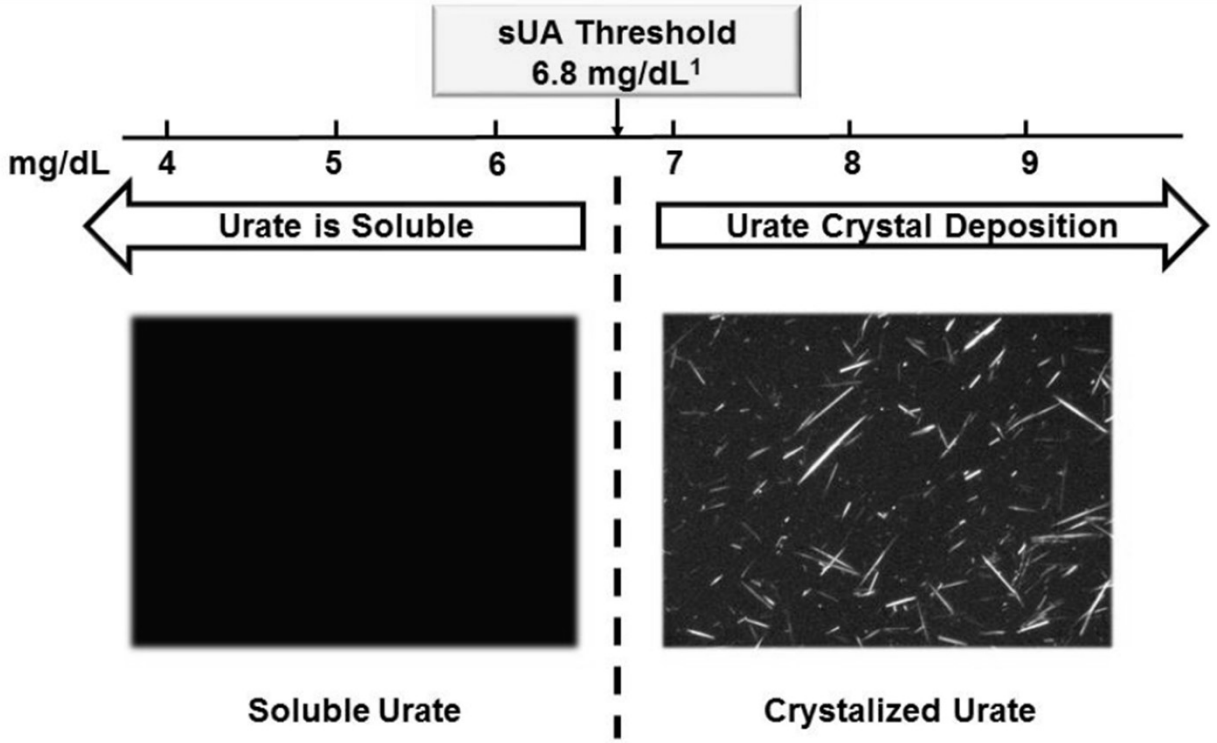


PATHOGENESIS OF URATE CRYSTAL DEPOSITION

- Limit of solubility of urate in serum is 6.8 mg/dl (WITHIN THE "NORMAL" range!)
  - Urate crystallizes as a monosodium salt in oversaturated joint tissues
  - At decreased temperature of periphery (e.g. feet), solubility is even less

CO-16

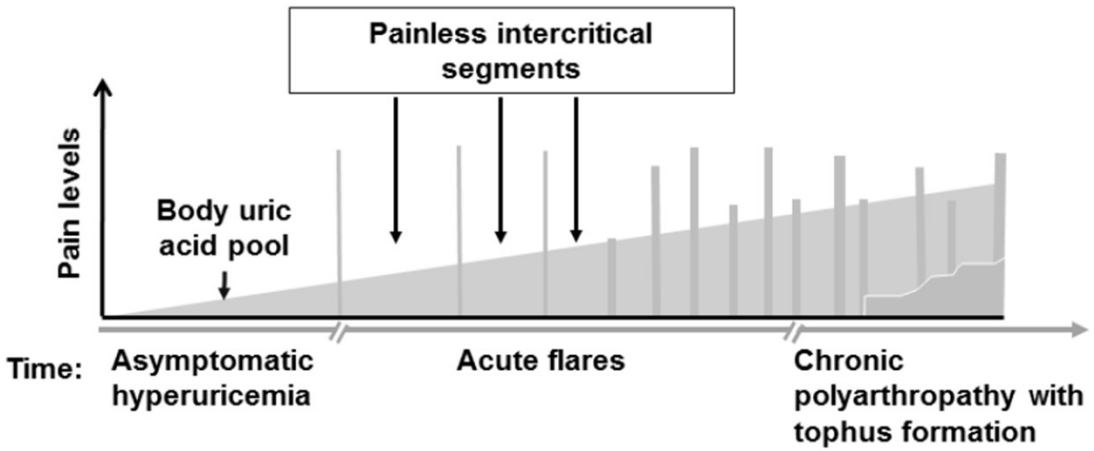
Solubility Threshold of Urate



1. Loeb, 1972.

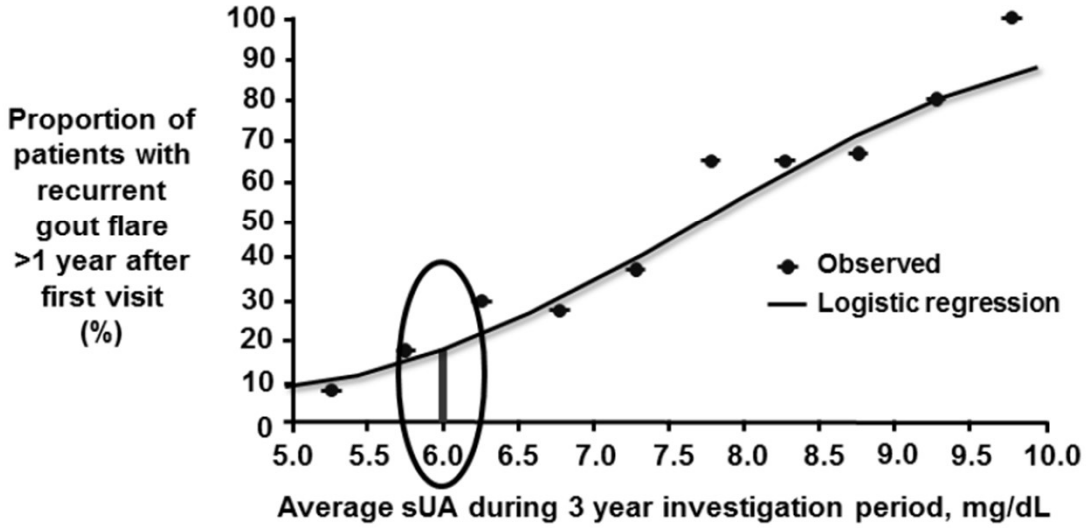
CO-18

Gout Develops and Progresses over Time as Uric Acid Load Increases



1. Doghramji, 2012.

Increase in Gout Flare Recurrence with Increasing sUA

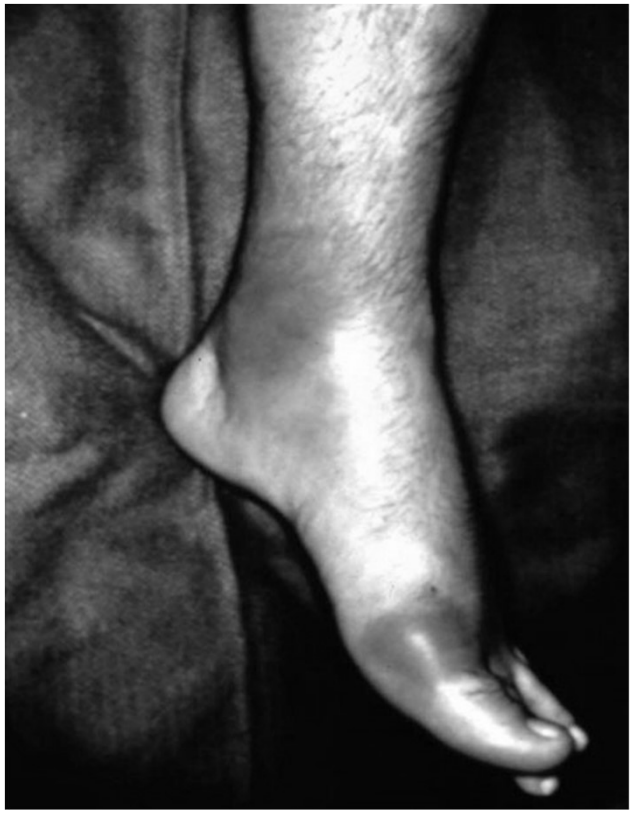


- 86% (71/81) of patients who had sUA <6.0 mg/dL did not experience acute flare during study period

Shoji, 2004.

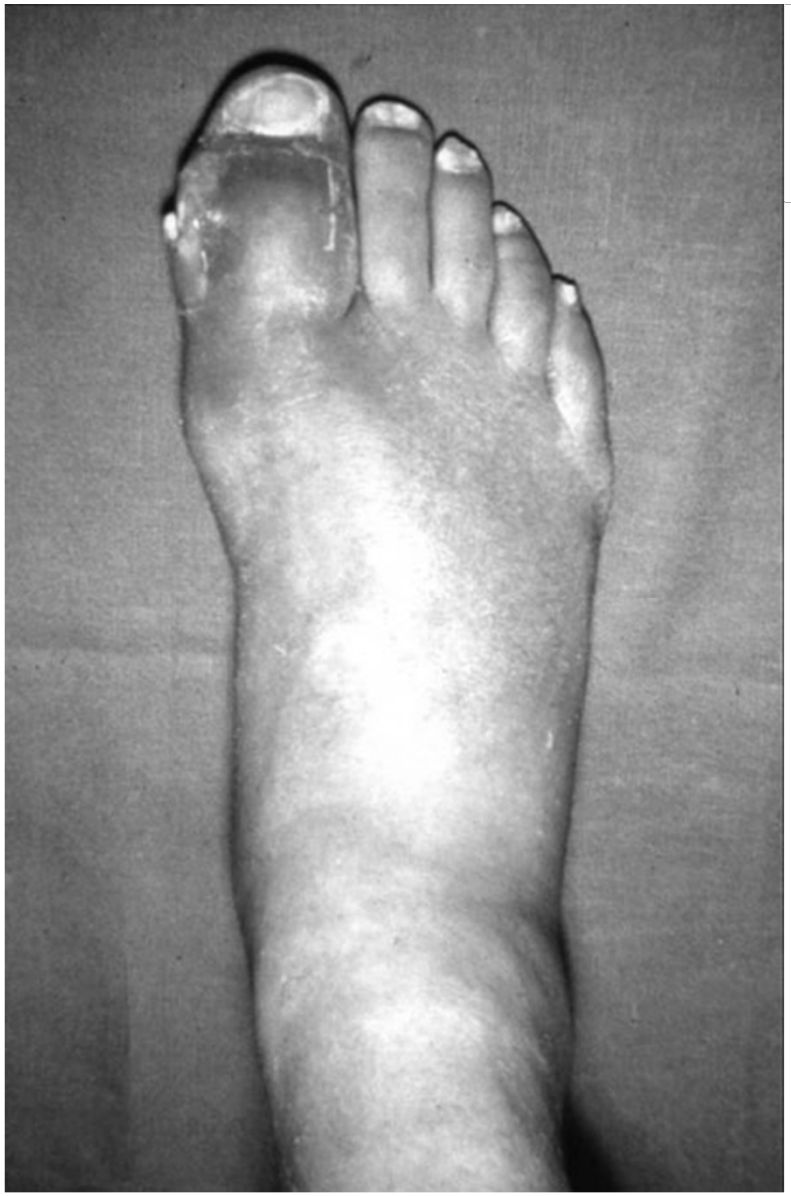
Acute Gouty Arthritis

ACUTE GOUT: PODAGRA

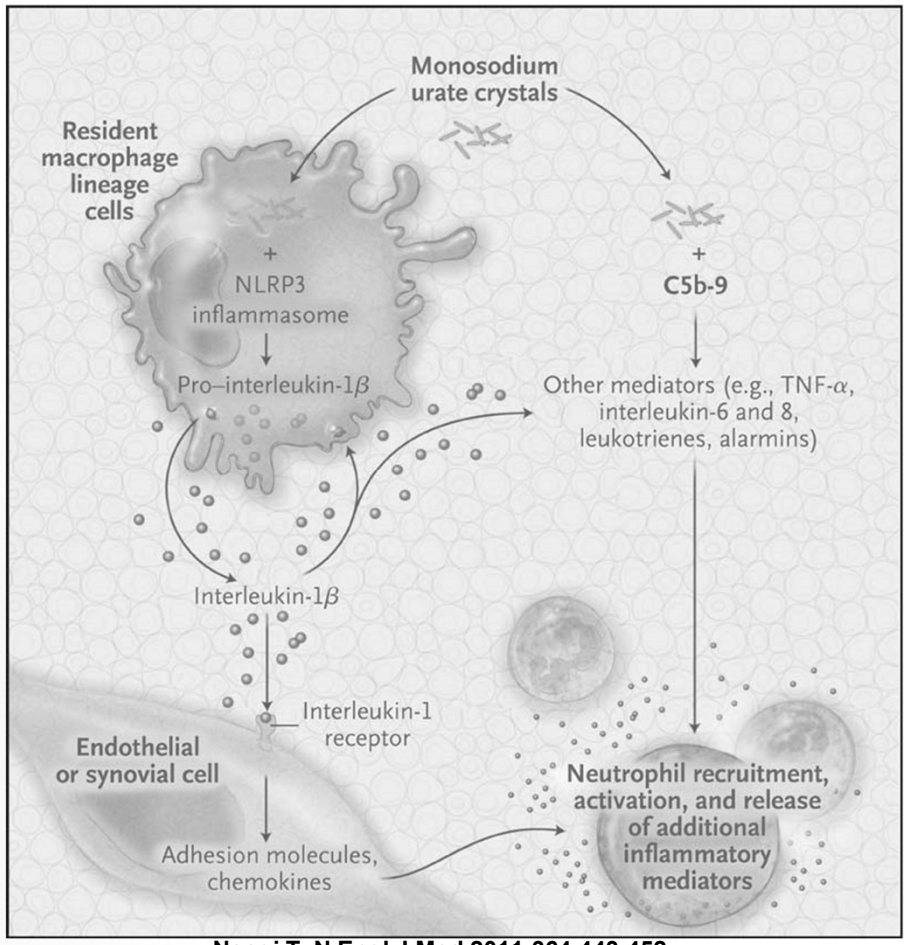


ACUTE GOUTY ARTHRITIS

- First MTP
- Desquamation from severe periarticular inflammation



Mechanisms of Inflammation in Gout.



Neogi T. N Engl J Med 2011;364:443-452

Pharmacologic Management Options for Acute Gout Attacks.

Table 1. **Pharmacologic Management Options for Acute Gout Attacks.**

Drug	Examples of Regimens from Randomized Clinical Trials	Alternative Regimens for Complete Attack Resolution*	Precautions
Nonsteroidal antiinflammatory drug†			Avoid in patients with renal or hepatic insufficiency, bleeding disorder, congestive heart failure, or allergy; associated with an increased risk of adverse thrombotic and gastrointestinal events; may be administered with a proton-pump inhibitor in patients at risk for gastrointestinal events.
Naproxen	500 mg orally twice daily for 5 days	375–500 mg orally twice daily for 3 days, then 250–375 mg orally twice daily for 4–7 days or until attack resolves	
Indomethacin	50 mg orally three times daily for 2 days, then 25 mg orally three times daily for 3 days	50 mg orally three times daily for 3 days, then 25 mg orally three times daily for 4–7 days or until attack resolves	
Colchicine	1.2 mg orally at first sign of gout flare, followed by 0.6 mg orally 1 hr later	Consider additional acute gout regimen to continue managing attack 12–24 hr after colchicine regimen (e.g., 0.6 mg of colchicine twice daily, a nonsteroidal antiinflammatory drug regimen, or an oral glucocorticoid regimen until attack resolves)	Avoid (or use lower dose) in older adults and those with renal insufficiency, hepatic dysfunction, or known gastrointestinal symptoms; adjust dose (and avoid in patients with renal or hepatic impairment) if used in conjunction with P-glycoprotein or CYP3A4 inhibitors (e.g., cyclosporine, clarithromycin, certain antiretroviral agents, certain antifungal agents, certain calcium-channel blockers, and grapefruit juice); avoid for gout-flare therapy in patients with renal or hepatic impairment who are already receiving colchicine prophylaxis; monitor for gastrointestinal symptoms, myotoxicity, and blood dyscrasias (details are available at www.fda.gov).
Oral glucocorticoids (prednisone or prednisolone)‡	Prednisolone, 30–35 mg daily for 5 days	Prednisone, 30–60 mg daily for 2 days (depending on severity of attack), then reduce by 5–10 mg every 2 days (depending on starting dose) in 10-day taper	Use caution in patients with hyperglycemia or congestive heart failure; may be used in patients with moderate-to-severe renal impairment.

* Longer durations of therapy may be necessary for patients with long-standing disease and severe flares.
† There are no published trials establishing the efficacy of celecoxib, the only selective cyclooxygenase-2 inhibitor available in the United States, for use in acute gout.
‡ Although there are insufficient data to recommend the use of intraarticular glucocorticoid injection, it may be a useful alternative for attacks that are limited to one or two joints and amenable to aspiration and in the absence of joint sepsis.

Neogi T. N Engl J Med 2011;364:443-452

The NEW ENGLAND JOURNAL of MEDICINE

“New” prescribing information on colchicine

Treatment of Acute Gouty Arthritis

- Colchicine is a plant alkaloid derived from the autumn crocus (Colchicum autumnale) First described by Greek surgeon Padanius Dioscorides around the year 60 CE
- Extracts in widespread use since early 1800
- Colchicine stops the microtubular formation of the inflammasome if given EARLY in the gout attack; not effective once the inflammasome has formed

Colcrys: Brand Name Colchicine

- FDA concerned that colchicine had never been formally approved for treatment of gout
- Also concerned about FATAL colchicine toxicity with standards doses
- *"Oral colchicine has been used for many years as an unapproved drug with no FDA-approved prescribing information, dosage recommendations, or drug interaction warnings"*
- Producers of colchicine were offered the opportunity to submit data for approval

DOSAGE AND ADMINISTRATION*

- **Gout Flares**: 1.2 mg (2 tablets) at the first sign of a gout flare followed by 0.6 mg (1 tablet) one hour later
- Higher doses have not been found to be more effective.
- The maximum recommended dose for treatment of gout flares is 1.8 mg over a 1 hour period.

- *package insert

DOSAGE AND ADMINISTRATION*

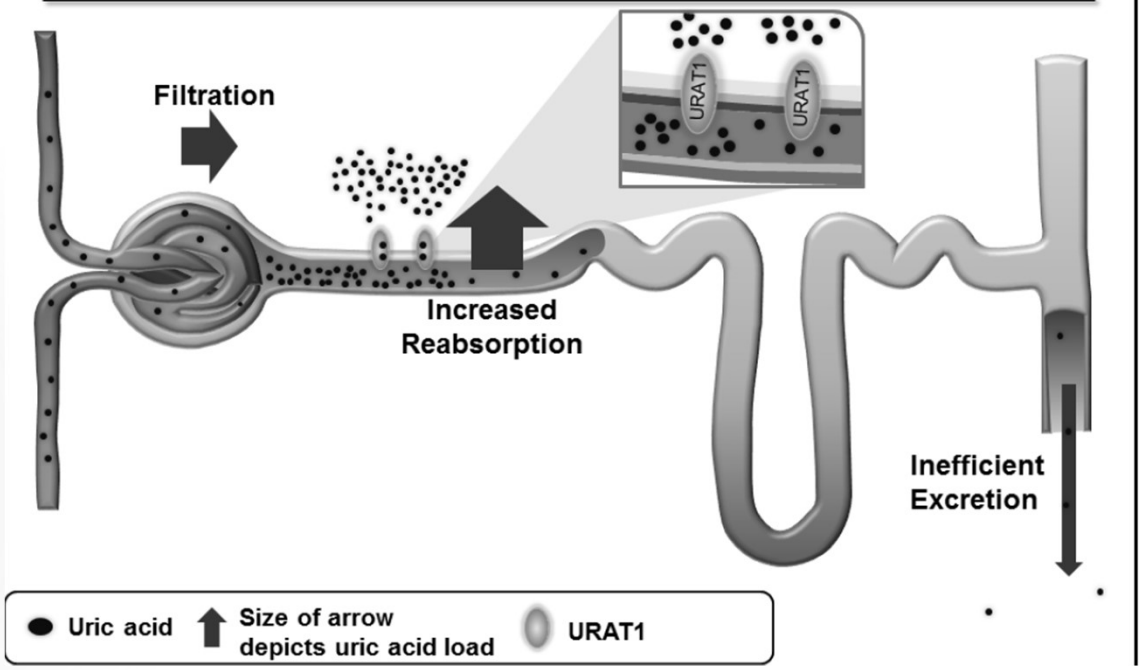
- In the presence of renal impairment, dosing for gout flares should be repeated no more than once every two weeks
- For patients undergoing dialysis, the total recommended dose for gout flares should be reduced to 0.6 mg (1 tablet) x 1 dose.
- For gout flares, a treatment course should be repeated no more than once every 2 weeks with no increase in dosage

- *package insert

Hyperuricemia

CO-95

Inefficient Excretion of Uric Acid in Patients with Gout



HYPERURICEMIA

- Underexcretion in 90%
  - Tubular secretion of urate decreased by
    - Thiazide diuretics (proximal tubule)
    - Salicylates (low dose)
    - Cyclosporine
      - Especially for cardiac transplantation
      - One in six patients with cyclosporine-induced hyperuricemia develop gout
      - Shorter asymptomatic period
    - Familial juvenile hyperuricemic nephropathy

Pharmacologic Options for Hyperuricemia Therapy in Gout.

Table 2. **Pharmacologic Options for Hyperuricemia Therapy in Gout.***

Drug	Example of Regimen	Considerations or Precautions
Urate-lowering therapy		Aim to maintain serum urate levels below 6 mg per deciliter, which requires regular monitoring and may require dose adjustments. Accompany the initiation of therapy with flare prophylaxis.
Xanthine oxidase inhibitor		Use in patients with urate overproduction or underexcretion. Avoid use (or monitor closely) in patients receiving azathioprine or 6-mercaptopurine because these drugs are metabolized by xanthine oxidase.
Allopurinol	Starting dose: 50–100 mg orally daily; increase dose every 2–4 wk to achieve serum urate target, with dose based on creatinine clearance; average daily dose, 300 mg, although many patients require higher doses	Use with caution in patients with renal insufficiency (based on creatinine clearance). The maximal dose may be as high as 800 mg daily, but there are limited data for doses above 300 mg daily. A mild rash occurs in approximately 2% of patients, and the risk is potentially increased by coadministration of ampicillin, amoxicillin, thiazide diuretics, or ACE inhibitors. Allopurinol hypersensitivity is rare, occurring in approximately 0.1% of patients, but can be fatal (rate of death, 20%). If the target serum urate level is not achieved, consider dose escalation beyond the level suggested by guidelines in patients with renal impairment (with close monitoring) or consider the use of an alternative therapy (e.g., febuxostat). Allopurinol can increase the anticoagulant effect of warfarin.
Febuxostat	Starting dose: 40 mg orally daily; increase to 80 mg orally daily after 2–4 wk to achieve serum urate target, if necessary†	Use as a second-line agent for patients who have contraindications or an inadequate response to allopurinol or uricosuric therapy. Although no dose adjustment is required for patients with mild-to-moderate renal or hepatic insufficiency, there are insufficient data for use in patients with a creatinine clearance of <30 ml per minute or severe hepatic impairment. Currently contraindicated for use with theophylline. Febuxostat has a higher cost than allopurinol.
Uricosuric agent (probenecid)‡	Starting dose: 250 mg orally daily; increase by 500 mg per mo to a maximal dose of 2–3 g per day (2 divided doses) in patients with normal renal function to achieve serum urate target	Avoid in patients with a history of nephrolithiasis and a creatinine clearance of <30 ml per minute. Adequate hydration is required to reduce risk of nephrolithiasis. The use of this drug can increase serum penicillin levels. Evaluate for renal uric acid excretion in patients with a family history of early onset of gout, onset of gout at <25 yr, or a history of nephrolithiasis, since this may identify patients with an overproduction of urate in whom uricosuric therapy should be avoided because of the risk of nephrolithiasis.
Uricase (pegloticase)	Intravenous infusion of 8 mg every 2 wk; requires premedication with antihistamines and glucocorticoids; start gout-flare prophylaxis ≥7 days before initiating treatment	Use for chronic gout in adults whose disease is refractory to conventional therapy (e.g., lack of normalization of serum urate, inadequate control of signs and symptoms with the use of a xanthine oxidase inhibitor at maximum medically appropriate dose, or other contraindication). There is a risk of infusion reactions (26%, vs. 5% in placebo group) even with premedication, particularly in patients without a therapeutic response (in whom serum urate levels increase to above 6 mg per deciliter, particularly on two consecutive occasions) or with antibodies against pegloticase. Anaphylaxis occurs in 5% of patients (vs. 0% in placebo group). No data are available regarding retreatment after stopping treatment for longer than 4 weeks. Do not use in patients with G6PD deficiency, and use caution in patients with congestive heart failure (insufficient safety data; some exacerbations in clinical trials). Cost is higher than for other therapies.
Flare prophylaxis during initiation of urate-lowering therapy		Aim to reduce the risk of flare during initial decrease in urate levels, presumably related to rapid mobilization of bodily urate stores. The duration of therapy is not well defined but treatment for at least 6 mo or until tophi resolve is recommended.
Colchicine	0.6 mg orally once or twice daily as tolerated	See Table 1 for precautions, particularly taking into account potential for increased toxic effects with prolonged therapy.
NSAID	Naproxen, 250 mg twice daily	See Table 1 for precautions, particularly taking into account potential for increased toxic effects with prolonged therapy. This drug has not been formally tested but has been used for prophylaxis in trials of urate-lowering therapies.

* ACE denotes angiotensin-converting enzyme, and NSAID nonsteroidal antiinflammatory drug.
† Febuxostat at a dose of 120 mg is available in Europe.
‡ Benzbromarone and sulfinpyrazone are available in a limited number of countries but not in the United States.

Neogi T. N Engl J Med 2011;364:443-452

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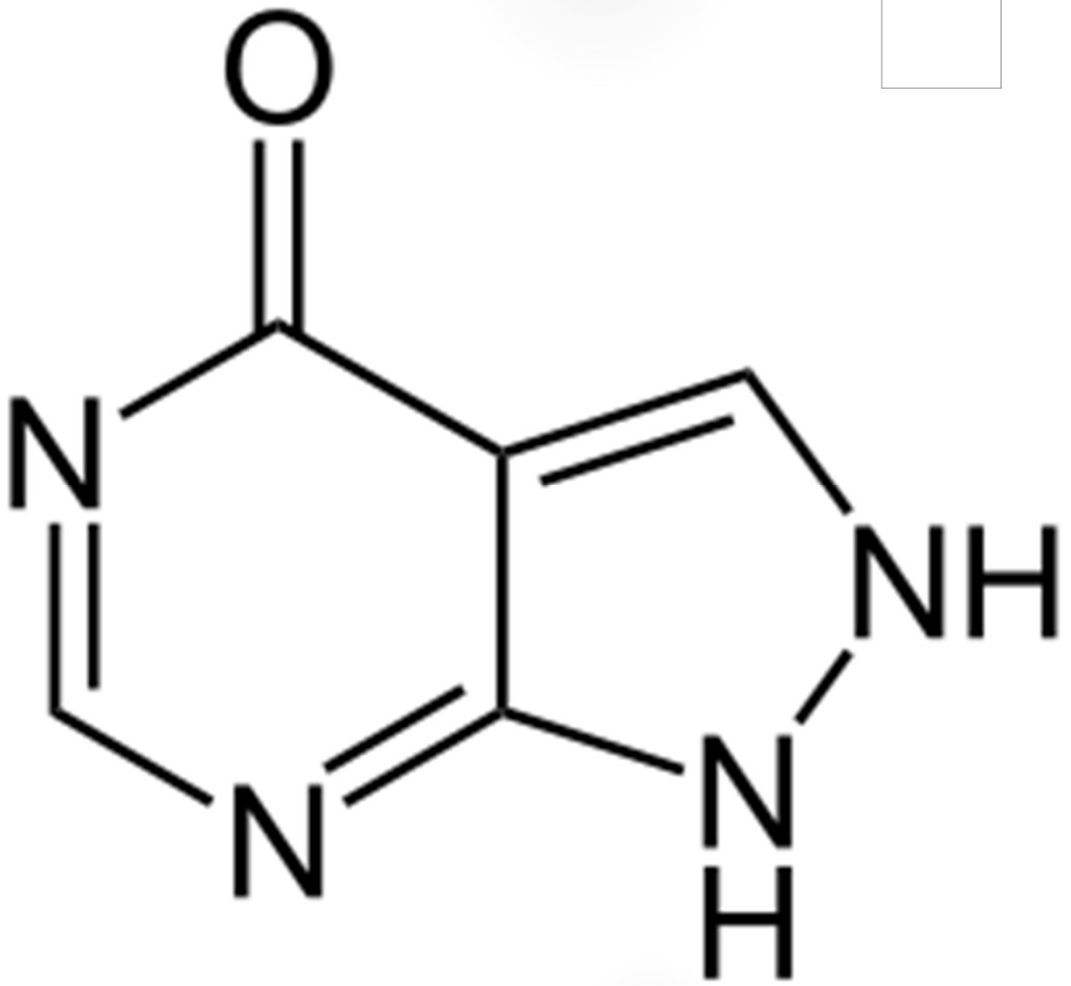
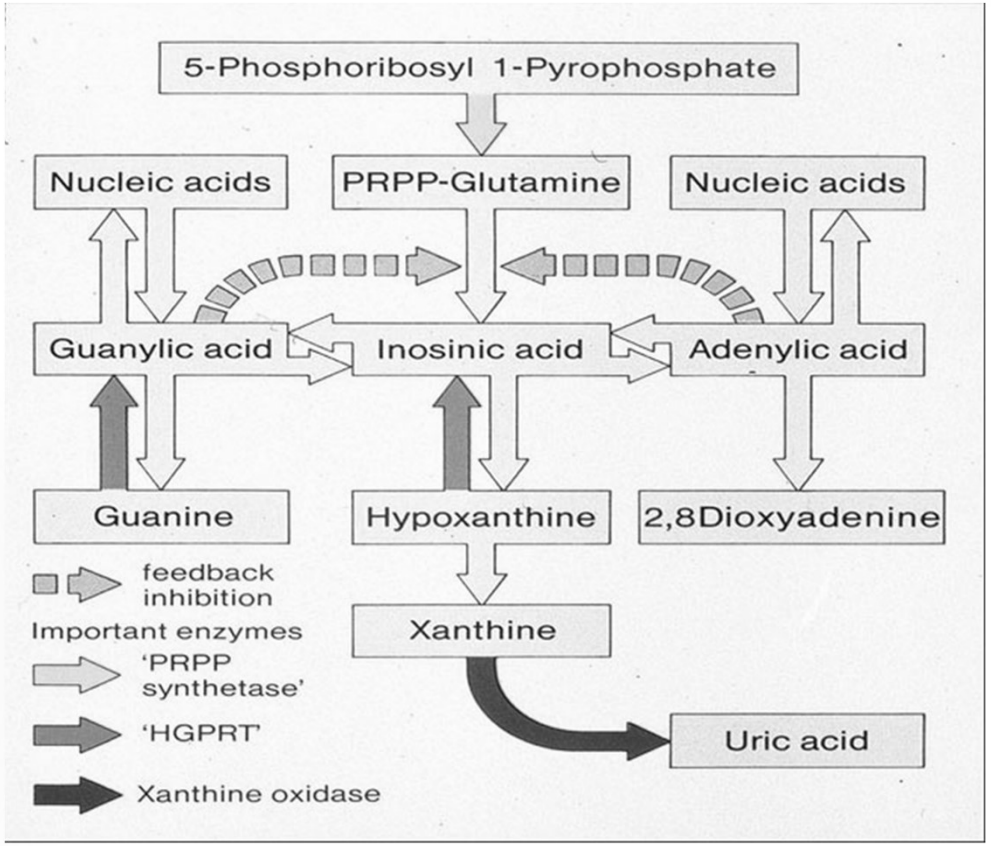
Allopurinol



PURINE METABOLISM



ALLOPURINOL

- Xanthine oxidase inhibitor
  - Blocks conversion of xanthine to uric acid
- Must use for
    - Overexcretors
    - Renal insufficiency
    - Nephrolithiasis
    - Tophi

The Controversy

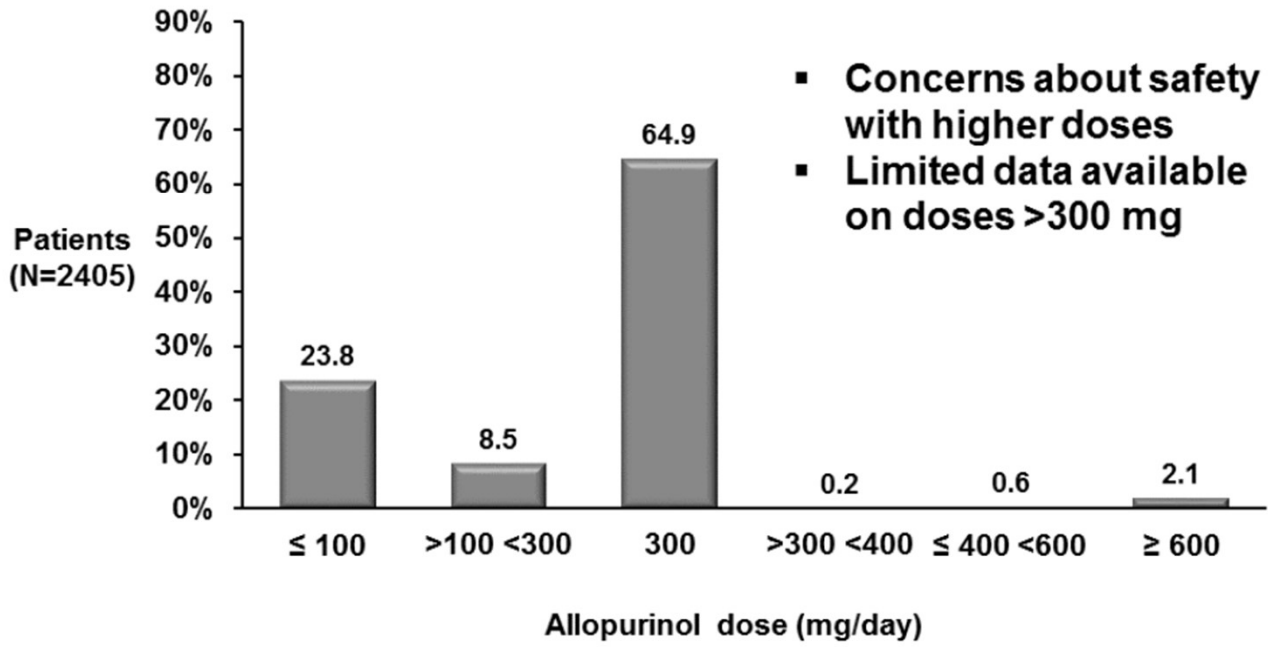
- ACP guidelines and ACR guidelines do not agree
  - ACR guidelines recommended “Treat to Target” (T2T)
  - ACP guidelines recommended “Treat to Avoid Symptoms” (T2AS)

Correct Dose of Allopurinol…

- FDA approved up to 800 mg a day
- The goal of treatment is not a "normal" UA, but rather a concentration of UA at which urate will not crystallize
- …is the dose which results in a **serum UA of** <6

CO-27

Allopurinol Doses >300 mg Rarely Prescribed



Sarawate, 2006.

Allopurinol

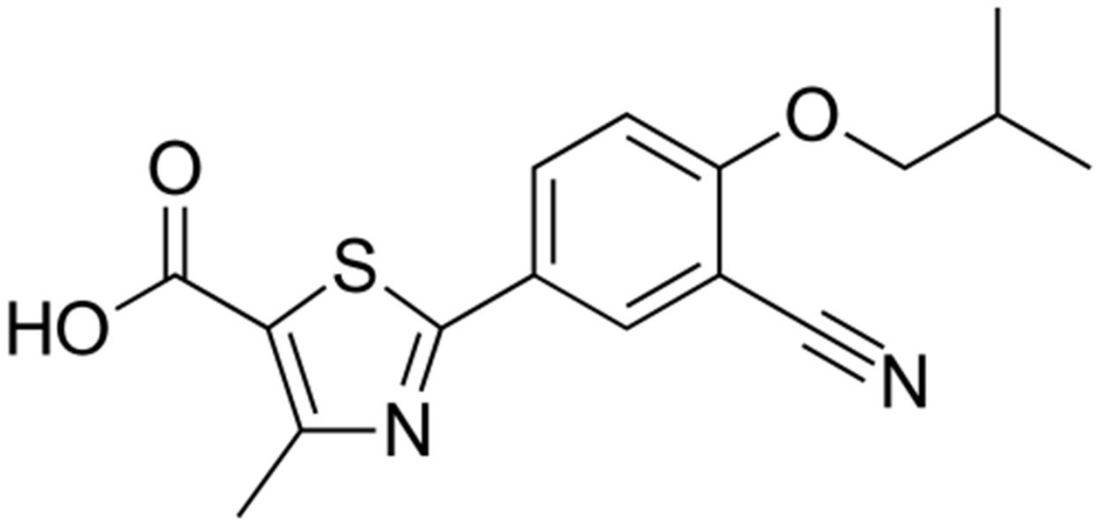
- Allopurinol hypersensitivity syndrome
  - Rare
  - Fever, rash, eosinophilia, hepatitis, renal failure
  - Can lead to death
  - More likely to occur in patients with CKD who are taking diuretics

Wortmann Curr Opin Rheumatol 2005; 17: 319-324.

Allopurinol Hypersensitivity Syndrome and HLA*B58:01

- HLA B*58:01
- Associated with Severe Cutaneous Adverse Reactions (SCAR), such as Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
- Individuals of Koreans, Han Chinese, and Thai descent
- This test is commercially available (Quest, Lab Corp)

Febuxostat



Febuxostat

- Chemically distinct from allopurinol
- Tolerated in patients sensitive to allopurinol
- Metabolized in the liver so dose adjustment not needed for CR CL >30 (no data for CR CL <30)

Febuxostat (continued)

- In a 4-week randomized, placebo-controlled study, 76% of gout patients receiving 80 mg daily …achieved serum uric acid levels <6.0, compared with 0% of those on placebo.

Becker *et al* Arthritis Rheum 2005; 52:916-923.

- Colchicine prophylaxis is needed during initiation of therapy

Febuxostat

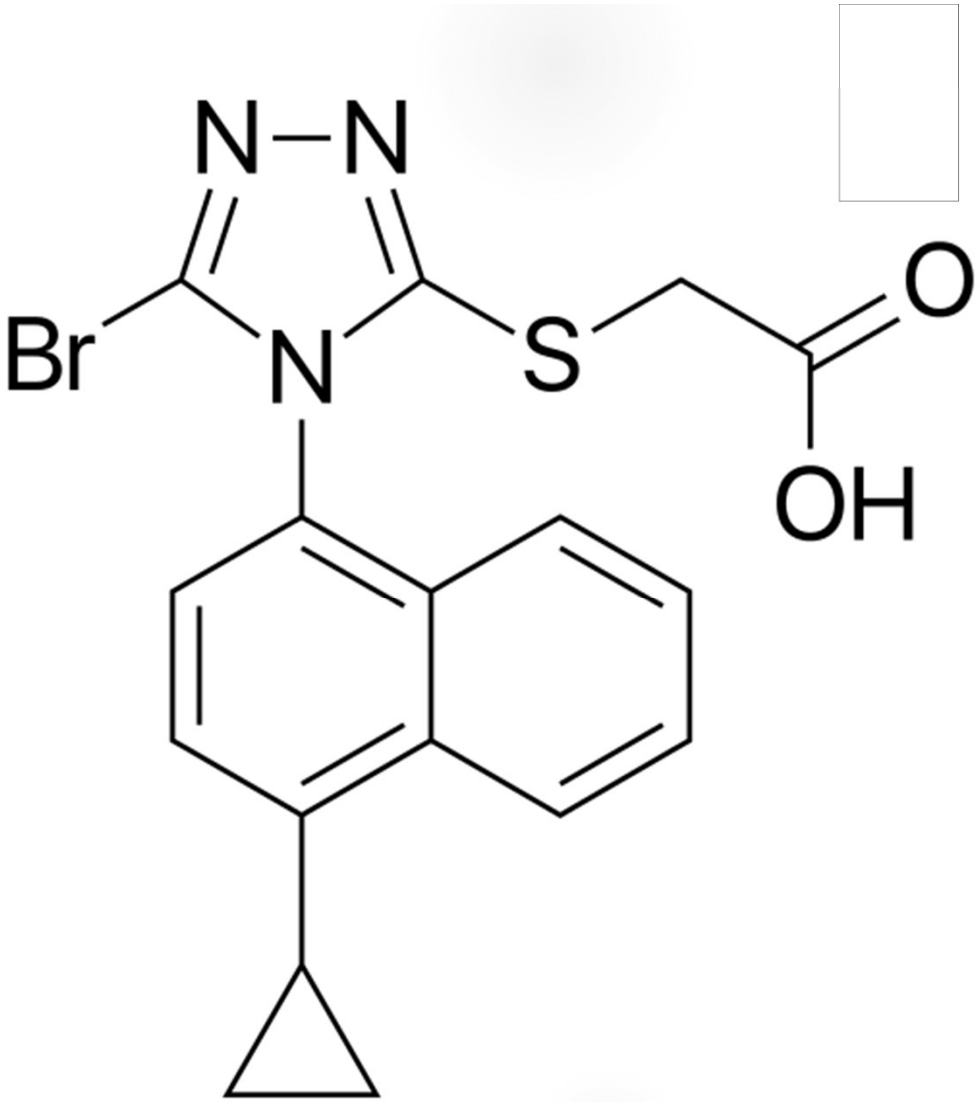
- Febuxostat 80 mg daily dosing shown to be more effective at achieving serum UA <6 than allopurinol 300 mg daily in a 52 week study in the U.S. and Canada

Becker *et al* N Engl J Med 2005; 353: 2450-2461.

Dosing of Febuxostat (Uloric)

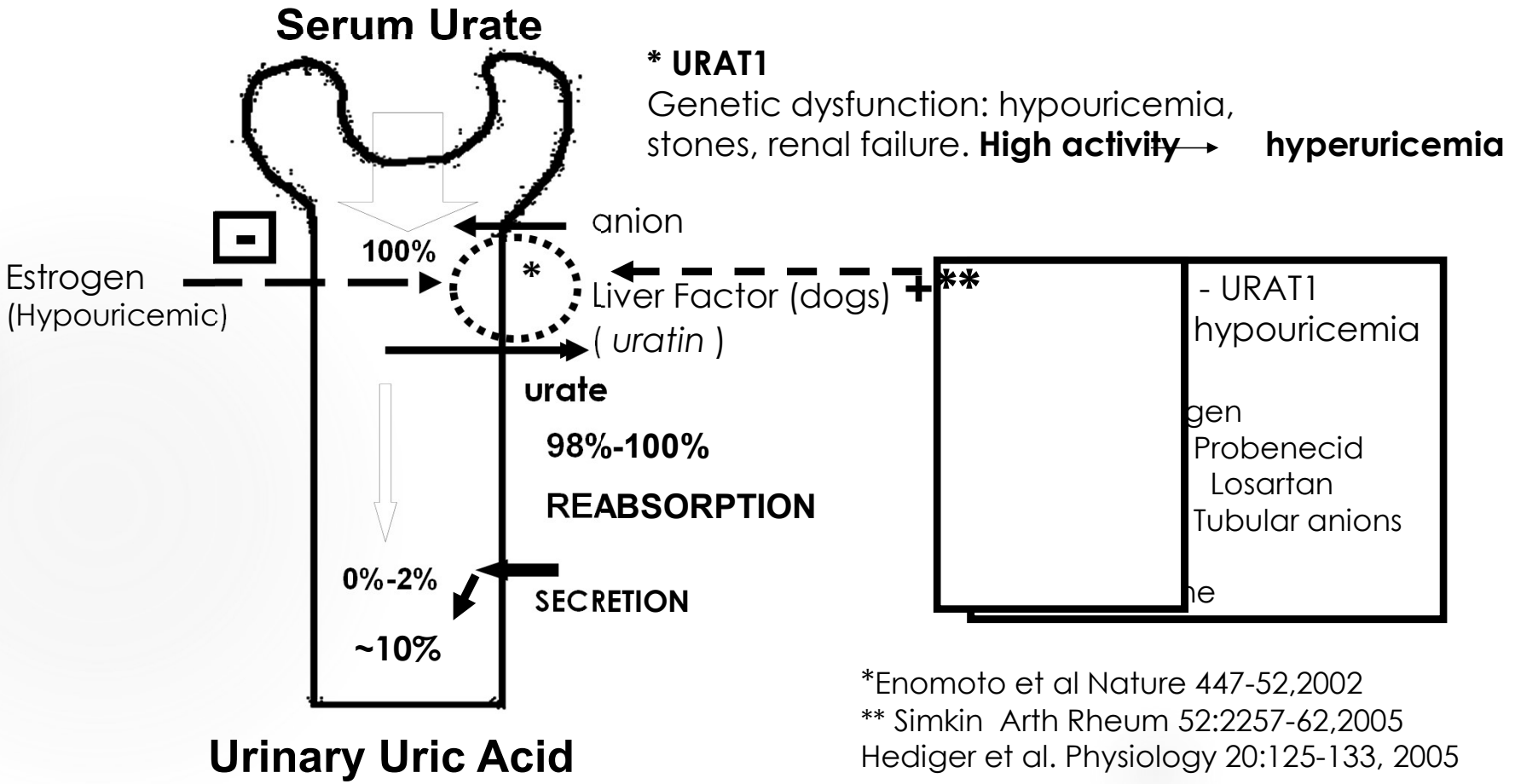
- Start at 40 mg daily
- Increase to 80 mg daily if serum UA is >6mg/dl after 2 weeks
- No data available
  - Doses > 80 mg/day
  - Use when Cr Cl < 30

Lesinurad



Renal Reabsorption of Uric Acid

URAT 1 (SLC22A12) Controls Serum Urate Level



*Enomoto et al Nature 447-52,2002
** Simkin Arth Rheum 52:2257-62,2005
Hediger et al. Physiology 20:125-133, 2005

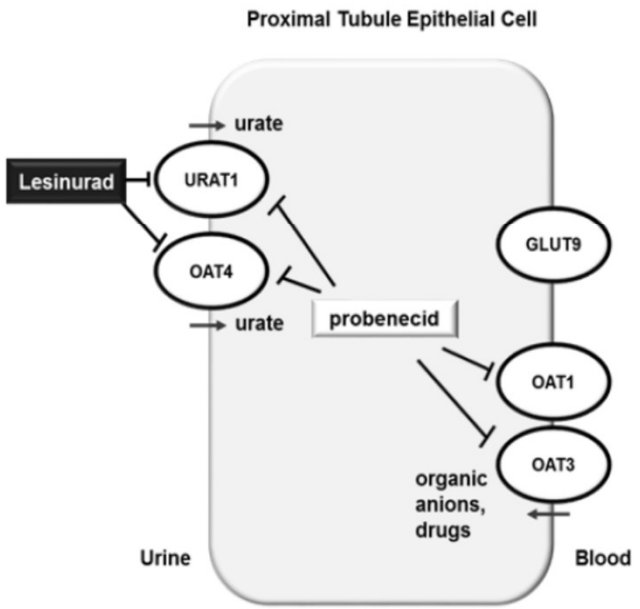
URAT1
RENAL URATE TRANSPORTER

- Anion exchanger
- In human proximal tubule cells (& smooth muscle)
- Oriented to reabsorb uric acid from tubule
- Genetic absence → uricosuria, hypouricemia, stones
- Inhibition → uricosuria, hypouricemia
  - Probenecid
  - Losartan
  - Benzbromarone
- Expression higher in male mice
  - Estrogen reduces synthesis

Reviewed in: Hediger et al. Physiology 20:125-133, 2005

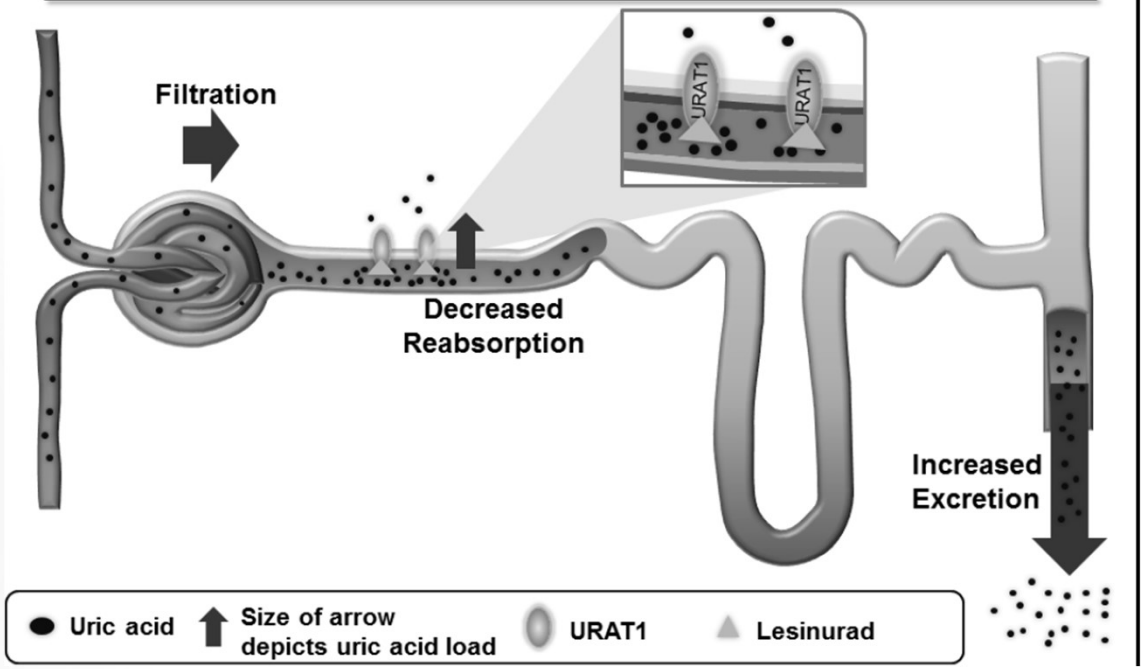
Lesinurad is Novel, Oral Urate Lowering Therapy for Uncontrolled Gout

- Only uric acid transporter 1 (URAT1) inhibitor in 60 yrs
  - URAT1 inhibition increases uric acid excretion, lowers sUA
- First selective uric acid reabsorption inhibitor
  - Inhibits URAT1 and organic anion transporter OAT4
  - Does not inhibit OAT1 and OAT3



CO-96

Lesinurad Increases Urinary Uric Acid Excretion



Lesinurad

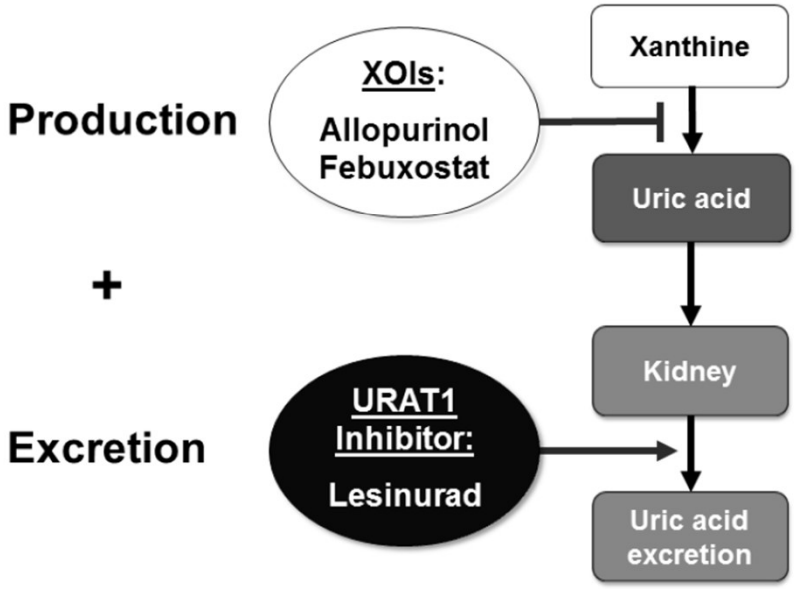
- Lesinurad is a uricosuric (selective uric acid reabsorption inhibitor) which was FDA approved in December 2015 for use at a dose of 200mg PO daily, in combination with a xanthine oxidase inhibitor (XOI)
- **Abstracts 206-209**: Lesinurad 12 month extension of several 12 month studies
  - Lesinurad 200 mg plus XOI and XOI alone had the comparable rates of AEs and renal AEs (kidney stones, rising creatinine); this did not change in the extension studies.
  - Adverse event rates were higher with lesinurad 400 mg daily plus XOI (c/w the other 2 groups), but this dose is not FDA approved.
  - Efficacy of XOI plus lesinurad 200 or 400mg persisted in the extension studies.

Lesinurad

- For patients on lesinurad 200mg or 400 mg daily in addition to a XOA in the extension trials
  - Tophi continued to shrink and resolve
  - Flares became increasingly rare
- **Conclusion:** The safety of lesinurad 200 mg po daily did not change over 2 years and the efficacy persisted.

CO-10

Dual Mechanism Approach: Lesinurad in Combination with XO Inhibitor



Lesinurad

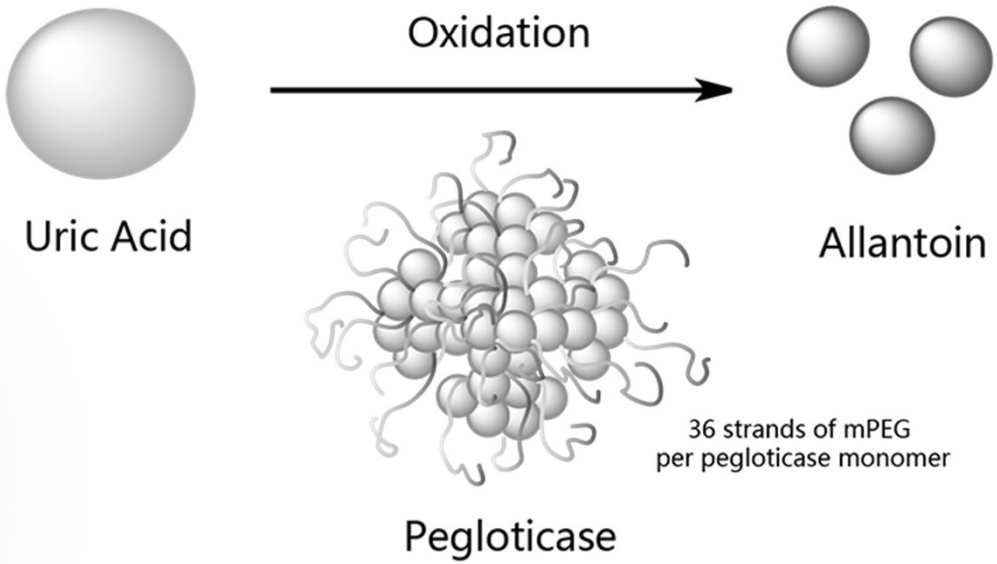
- #206 Terkeltaub R, Malamet R, Bos K, Li J, Goldfarb D, Pillinger M, Jalal D, Hu J, Saag K. Renal Safety of Lesinurad: A Pooled Analysis of Phase III and Extension Studies [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10). http://acrabstracts.org/abstract/renal-safety-of-lesinurad-a-pooled-analysis-of-phase-iii-and-extension-studies/.
- #207 Becker MA, Keenan RT, Khanna P, Malamet R, Bos K, Li J, Hu J, White W. Integrated Safety of Lesinurad, a Novel Uric Acid Reabsorption Inhibitor for the Treatment of Gout [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10). http://acrabstracts.org/abstract/integrated-safety-of-lesinurad-a-novel-uric-acid-reabsorption-inhibitor-for-the-treatment-of-gout/
- #208 Saag K, Becker MA, Storgard C, Fung M, Hu J, Bardin T. Examination of Serum Uric Acid (sUA) Lowering and Safety with Extended Lesinurad + Allopurinol Treatment in Subjects with Gout [abstract]. *Arthritis Rheumatol.* 2016; 68 (suppl 10). http://acrabstracts.org/abstract/examination-of-serum-uric-acid-sua-lowering-and-safety-with-extended-lesinurad-allopurinol-treatment-in-subjects-with-gout/.
- #209 Bardin T, Dalbeth N, Terkeltaub R, Storgard C, Fung M, Hu J, Perez-Ruiz F. Clinical Response of Tophus and Flares to Extended Use of Lesinurad in Combination with a Xanthine Oxidase Inhibitor in Patients with Gout [abstract]. Arthritis Rheumatol. 2016; 68 (suppl 10). http://acrabstracts.org/abstract/clinical-response-of-tophus-and-flares-to-extended-use-of-lesinurad-in-combination-with-a-xanthine-oxidase-inhibitor-in-patients-with-gout/.

PARADOX OF TREATMENT

- Rapid reduction urate levels can precipitate acute attack
  - Destabilization of microtophi in the gouty synovium, releasing urate crystals into synovial fluid
  - PMNs are more efficient in phagocytosis of crystals at lower urate concentrations
- Prophylactic colchicine or NSAIDs useful during the first few months of treatment

DO NOT STOP A URATE LOWERING DRUG DURING AN ACUTE ATTACKOF GOUT!!

Pegloticase



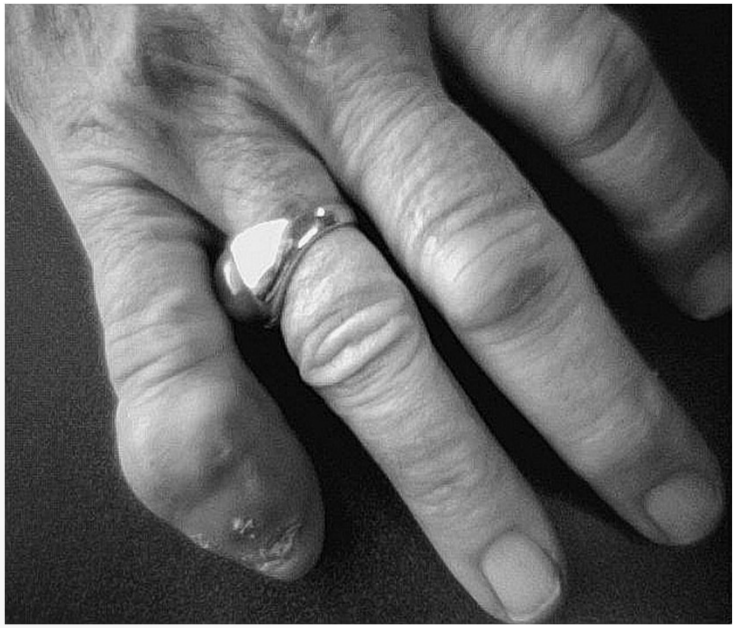
Uricase

- Uricase is an enzyme found in most non-primate mammals that converts relatively insoluble uric acid to allantoin, which is more soluble.
  - Foreign protein which can cause hypersensitivity reactions, including anaphylaxis, with repeated exposure
  - Can cause hemolysis and methemoglobinemia in G6PD deficiency

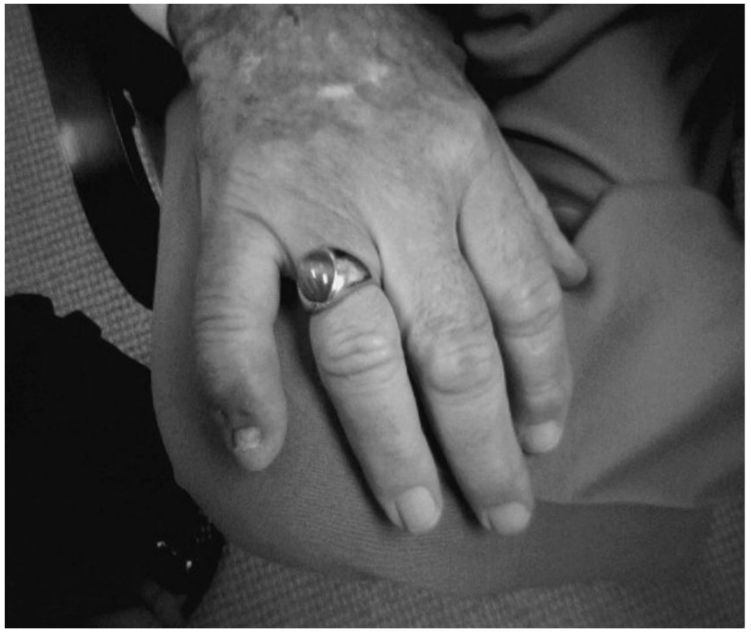
Krystexxa (pegloticase) administration

- 8 mg IV over 2 hours every 2 weeks
- Monitor serum uric acid levels before administration
  - D/C treatment if 2 UA levels > 6 mg/dl
  - Rising UA levels suggests antibody formation to medication
- Pre-medicate with antihistamines and corticosteroids
- Be prepared to manage anaphylaxis

Pegylated Uricase Therapy for Tophacious Gout



May, Pretreatment



July, 2 months post-treatment

Indications for Urate Lowering Medications

- Frequent and disabling attacks of gout
- Clinical or radiographic signs of chronic gouty joint disease
- Presence of tophaceous deposits
- Gout with renal insufficiency
- Recurrent nephrolithiasis
- Serum urate levels persistently >13 mg/dl in men or >10 mg/dl in women
- Urinary uric acid excretion >1100 mg/day
- Impending cytotoxic chemotherapy or XRT for leukemia or lymphoma

Adapted from Up to Date.

ACP Guidelines

- Annals of Internal Medicine November 1, 2016
- Standard literature review
  - Agency for Healthcare Research and Quality (AHRQ)-funded
  - ACP-directed
  - Geared guidelines to primary care providers (PCPs)
    - Excluded meds that PCPs are unlikely to prescribe, *e.g.* IL-1 inhibitors and pegloticase
    - Included febuxostat studies

ACP Guidelines

- ACP Guidelines for Management of Hyperuricemia in the Gout Patient
- ***Recommended treating to avoid symptoms [not to a particular serum uric acid (sUA) level] and therefore did not recommend monitoring sUA levels.***

"Management of Gout: A Systematic Review in Support of an ACP Clinicial Practice Guideline"

- …"the *hypothesis* that lower serum urate levels are causally associated with a lower rate of acute gout attacks."
- "..no direct evidence supports or refutes the values of such monitoring" (referring to monitoring the serum urate levels in the context of administering ULT)
- "The evidence base for use of serum urate level as a target value for treatment is limited by the lack of any trial that has based treatment decision on different specific targets (such as a target of 7.0 vs 6.0 mg/dl) or any target as opposed to treating symptoms…The value of such a strategy has yet to be proved"
- "Thus, despite the strong biologic appeal of such a strategy and its advocacy by major specialty society guidelines*, we judged the strength of evidence for monitoring to be low"

- *American College of Rheumatology, European League Against Rheumatism, British Society for Rheumatology and British Health Professionals in Rheumatolgy Standards
- Ann Intern Med. 2017;166:37-51. doi:10:10.7326/M16-0461

The Controversy

- ACP guidelines do not agree with the ACR guidelines
  - ACR guidelines recommended “Treat to Target” (T2T)
  - ACP guidelines recommended “Treat to Avoid Symptoms” (T2AS)

"To Treat or Not to Treat (to Target) in Gout"

- "Hyperuricemia is...the main pathophysiologic culprit that causes flares, tophi, and joint damage; therefore, management of hperuricemia is a key tenet of disease control"
- "When patients never receive ULT or receive inappropriately low doses, ongoing urate deposition occurs, leading to progression of tophaceous deposits, further joint damage, and functional limitations"
- "…for patients who start allopurinol therapy without a hypersensitivity reaction in the first 180 days or so, the likelihood of developing a reaction later is exceedingly low"

- Ann Intern Med. 2017:166:71-72. doi:10.7326/M16-2401

Arguments Favoring T2T over T2AS

- Knowing that urate is soluble below 6.8mg/dl, it is likely that the reduction in gout flares at sUA <6 was because of the sUA level and not some other factor.
- Based on the solubility of urate, a target of <6 is reasonable.
- There is evidence that low sUA levels are not harmful, so the analogy to reducing glucose or raising hemoglobin is not valid
  - In the Pegloticase trials, patients tolerated sUA levels of 1-2mg/dl without observed adverse effects
  - At the turn of the 20th century, mean sUA levels in the US population were 3-4mg/dl, well below what is typically achieved with ULT in gout patients.