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
Gout is Urate Crystal Deposition Disease

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

\textsuperscript{1} Zhu, 2011. \textsuperscript{2} Vazquez-Mellado, 2007.
Serious Comorbidities Associated with Gout

Increased Risk of CV Death Associated with Gout

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

- All-cause mortality: 1.28 (1.15-1.41)
- All cardiovascular death: 1.38 (1.15-1.66)
- Fatal coronary heart disease: 1.55 (1.24-1.93)

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

1. Glomerular filtration of all serum urate

2. Proximal tubular resorption of 99% of filtered load

3. Resecretion of 50% of resorbed load

4. Resorption of about 80% of resecreted urate

5. Excretion of about 10% of filtered load (approx. 600 mgms/day)
Normal Renal Handling of Uric Acid
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
Solubility Threshold of Urate

sUA Threshold
6.8 mg/dL

mg/dL
4 5 6 7 8 9

Urate is Soluble

Urate Crystal Deposition

Soluble Urate

Crystalized Urate

Gout Develops and Progresses over Time as Uric Acid Load Increases

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

Acute Gouty Arthritis
ACUTE GOUT: PODAGRA
ACUTE GOUTY ARTHRITIS

- First MTP
- Desquamation from severe periarticular inflammation
## Pharmacologic Management Options for Acute Gout Attacks.

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<td>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 <a href="http://www.fda.gov">www.fda.gov</a>).</td>
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<td>Oral glucocorticoids (prednisone or prednisolone)‡</td>
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* 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.
“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 standard 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
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.

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<td>Urate-lowering therapy</td>
<td></td>
<td>Aim to maintain serum urate levels below 6 mg per dl, which requires regular monitoring and may require dose adjustments. Accompany the initiation of therapy with flue prophylaxis.</td>
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<td>Xanthine oxidase inhibitor</td>
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<td>Use in patients with urate overproduction or undersecretion. Avoid use (or monitor closely) in patients receiving azathioprine or 6-mercaptopurine because these drugs are metabolized by xanthine oxidase.</td>
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<td>Allopurinol</td>
<td>Starting dose: 50-100 mg orally daily; increase dose every 1-2 weeks to achieve serum urate target, with dose based on creatinine clearance; average daily dose, 100 mg, although many patients require higher doses</td>
<td>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, aminoglycosides, 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, and may require dose adjustment.</td>
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<td>Febuxostat</td>
<td>Starting dose: 40 mg orally daily; increase to 80 mg orally daily after 2-4 weeks to achieve serum urate target, if necessary</td>
<td>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 &lt;30 ml per minute or severe hepatic insufficiency. Currently contraindicated for use with cyclophosphamide. Febuxostat has a higher cost than allopurinol.</td>
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<td>Uricosuric agent (probencid)</td>
<td>Starting dose: 250 mg orally daily; increase by 500 mg per day to a maximal dose of 2-3 g per day (2 divided doses) in patients with normal renal function to achieve serum urate target</td>
<td>Avoid in patients with a history of nephrolithiasis and a creatinine clearance of &lt;10 ml per minute. Adequate hydration is required to reduce risk of nephrolithiasis. The use of this drug can increase serum uric acid levels. Evaluate for renal and acid excretion in patients with a family history of early onset of gout, onset of gout at &lt;25 yr, or a history of nephrolithiasis, since this may identify patients at risk for nephrolithiasis. Inform patients that uicosuric therapy should be avoided because of the risk of nephrolithiasis.</td>
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<td>Uricase (peptidase)</td>
<td>Intravenous infusion of 8 mg every 2 wk; requires premedication with antihistamines and glucocorticoids; start flue prophylaxis 7 days before initiating treatment</td>
<td>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 (20%, vs. 3% in placebo group) even with premedication, particularly in patients without a therapeutic response (in whom serum urate levels increase to above 8 mg per deciliter, particularly in two consecutive occasions) or with antibodies against peptidase. Anaphylaxis occurs in 3% of patients (vs. 0% in placebo group). No data are available regarding retreatment after stopping treatment for longer than 6 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.</td>
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<td>Flue prophylaxis during initiation of urate-lowering therapy</td>
<td>Aim to reduce the risk of flue during initial increase in urate levels, presumably related to rapid mobilization of body urate stores. The duration of therapy is not well defined but treatment for at least 6 mos or until target level is achieved is recommended</td>
<td>See Table 1 for precautions, particularly taking into account potential for increased toxic effects with prolonged therapy.</td>
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<td>Colchicine</td>
<td>0.6 mg orally once or twice daily as tolerated</td>
<td>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 therapy.</td>
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<td>NSAO</td>
<td>Naproxen, 250 mg twice daily</td>
<td>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 therapy.</td>
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ACE denotes angiotensin-converting enzyme, and NSAO nonsteroidal anti-inflammatory drug.
† Febuxostat at a dose of 120 mg is available in Europe.
‡ Berenil, narcorin, and sulfisoxazole are available in a limited number of countries but not in the United States.

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
Allopurinol Doses >300 mg Rarely Prescribed

- Concerns about safety with higher doses
- Limited data available on doses >300 mg

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

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)
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.


Colchicine prophylaxis is needed during initiation of therapy.
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.

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

URAT1
Genetic dysfunction: hypouricemia, stones, renal failure. **High activity** → **hyperuricemia**

* Estrogen (Hypouricemic)

100%

Liver Factor (dogs) (uratin)

** - URAT1 hypouricemia

- Estrogen
- Probenecid
- Losartan
- Tubular anions

98%-100%

REABSORPTION

0%-2%

~10%

SECRETION

Urine Uric Acid

** 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

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
Lesinurad Increases Urinary Uric Acid Excretion

Filtration

Decreased Reabsorption

Increased Excretion

- Uric acid
- Size of arrow depicts uric acid load
- URAT1
- 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.
Dual Mechanism Approach: Lesinurad in Combination with XO Inhibitor

Production

XOIs: Allopurinol Febuxostat

+ Xanthine

Uric acid

Kidney

URAT1 Inhibitor: Lesinurad

Uric acid excretion

Excretion
Lesinurad


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 ATTACK OF GOUT!!
Pegloticase

Uric Acid → Oxidation → Allantoin

36 strands of mPEG per pegloticase monomer
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.**
…”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 Rheumatology Standards

The Controversy

- ACP guidelines do not agree with the ACR guidelines
  - ACR guidelines recommended “Treat to Target” (T2T)
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“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 hyperuricemia is a key tenet of disease control.”

“...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”

Disclosures

- None relate to this presentation
- Consultant
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- Speaking
  - Pfizer
  - Novartis
  - Mallinckrodt
  - Celgene
- Clinical Trial Support
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Lower Risk of Death  |  Higher Risk of Death

BRIEF review of the essentials

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  - 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
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2. Proximal tubular resorption of 99% of filtered load

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- Filtration
- Reabsorption
- Excretion

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- Desquamation from severe periarticular inflammation
Mechanisms of Inflammation in Gout.
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‡ 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.

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“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
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>
<thead>
<tr>
<th>Drug</th>
<th>Example of Regimen</th>
<th>Considerations or Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urate-lowering therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Xanthine oxidase inhibitor</td>
<td>Use in patients with urate overproduction or undersecretion. Avoid use (or monitor closely) in patients receiving aminopyrine or 6-mercaptopurine because these drugs are metabolized by xanthine oxidase.</td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Starting dose: 100–100 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.</td>
<td>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 hyperuricosuria is rare, occurring in approximately 0.1% of patients, but can be fatal (rate of death, 10%). 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.</td>
</tr>
<tr>
<td>Febuxostat</td>
<td>Starting dose: 40 mg orally daily; increase to 80 mg orally daily after 2–4 wk to achieve serum urate target, if necessary.</td>
<td>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 &lt;30 ml per minute or severe hepatic impairment. Current contraindicated for use with methotrexate. Febuxostat has a higher cost than allopurinol.</td>
</tr>
<tr>
<td>Uricosuric agent (probencid)</td>
<td>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.</td>
<td>Avoid in patients with a history of nephrolithiasis and a creatinine clearance of &lt;30 ml per minute. Adequate hydration is required to reduce risk of nephrolithiasis. The use of this drug can increase serum parapsin levels. Evaluate for renal and acid excretion in patients with a family history of early onset of gout, onset of gout at &gt;45 yr, or a history of nephrolithiasis, since this may identify patients with an increased risk of adverse effects. Uricosuric therapy should be avoided because of the risk of nephrolithiasis.</td>
</tr>
<tr>
<td>Uricase (allopurinolase)</td>
<td>Intravenous infusion of 8 mg every 2 wk; requires premedication with antihistamines and glucocorticoids; start gout/urate prophylaxis 7 days before initiating treatment.</td>
<td>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. 3% in placebo group) even with premedication, particularly in patients without a therapeutic response (e.g., serum urate levels increase to above 6 mg per deciliter, particularly on two consecutive occasions) or with antibodies against allopurinolase. Anaphylaxis occurs in 3% of patients (vs. 0% in placebo group). No data are available regarding retreatment after stopping treatment for longer than 4 wk. 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.</td>
</tr>
<tr>
<td>Flare prophylaxis during initiation of urate-lowering therapy</td>
<td>Aim to reduce the risk of flares during initial dose increase of urate levels, presumably related to rapid mobilization of body’s urate stores. The duration of therapy is not well defined but treatment for at least 6 mos or until urate level is tolerated.</td>
<td>See Table 2 for precautions, particularly taking into account potential for increased toxic effects with prolonged therapy.</td>
</tr>
<tr>
<td>Colchicine</td>
<td>0.6 mg orally once or twice daily as tolerated. See Table 2 for precautions, particularly taking into account potential for increased toxic effects with prolonged therapy.</td>
<td></td>
</tr>
<tr>
<td>NSAID</td>
<td>Naproxen, 500 mg twice daily. See Table 2 for precautions, particularly taking into account potential for increased toxic effects with prolonged therapy.</td>
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</tr>
</tbody>
</table>

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

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
Allopurinol Doses >300 mg Rarely Prescribed

- Concerns about safety with higher doses
- Limited data available on doses >300 mg

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

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)
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.


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

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

Serum Urate
* URAT1
Genetic dysfunction: hypouricemia, stones, renal failure. High activity → hyperuricemia

Urinary Uric Acid
0%-2% REABSORPTION

- Estrogen (Hypouricemic)
- Liver Factor (dogs) (uratina)
- Probenecid, Losartan
- Ketone
- ASA

- URAT1 hypouricemia
- Liver Factor (dogs)
- Losartan
- Tubular anions

** 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 (and smooth muscle)
- Oriented to reabsorb uric acid from tubule
- Genetic absence ➔ uricosuria, hypouricemia, stones
- Inhibition ➔ uricosuria, hypouricemia
  - Probenecid
  - Losartan
  - Benz bromarone
- Expression higher in male mice
  - Estrogen reduces synthesis

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
Lesinurad Increases Urinary Uric Acid Excretion
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.
Dual Mechanism Approach: Lesinurad in Combination with XO Inhibitor

Production

XOIs: Allopurinol Febuxostat

+ 

Excretion

URAT1 Inhibitor: Lesinurad

Xanthine

Uric acid

Kidney

Uric acid excretion
Lesinurad


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 ATTACK OF GOUT!!
Pegloticase

Uric Acid → Oxidation → Allantoin

Pegloticase

36 strands of mPEG per pegloticase monomer
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 Clinical 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

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 hyperuricemia 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”

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.