Gout and Hyperuricemia: Perceptions and Realities

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Learning Objectives

- Describe the prevalence and pathophysiology of gout
- Discuss gout comorbidities, and the long-term consequences of untreated gout
- Diagnose and manage all stages of hyperuricemia and gout
Gout Is a Urate Crystal Deposition Disease

- Most common cause of inflammatory arthritis in adults, affecting 8.3 million patients in the US
- Caused by hyperuricemia, primarily due to inefficient excretion of uric acid
- Crystal deposition in joints and soft tissues can lead to
  - Inflammation
  - Acute gout flares
  - Tophi
  - Long-term bone and joint damage
  - Associated with increased risk of renal comorbidities
- Mounting evidence that gout and crystal deposition can be associated with cardiovascular and metabolic diseases; however, causality has not been proven
- If untreated, ~70% of patients progress to tophaceous gout within 20 years

Images courtesy of Dr. Fernando Perez-Ruiz, Cruces University Hospital, Barakaldo, Spain.

Physiologic Definition of Hyperuricemia

Hyperuricemia defined as >6.8 mg/dL

sUA=serum urate.

Managing Hyperuricemia

- Uric acid-lowering drugs are not indicated for the management of asymptomatic hyperuricemia, **but don’t ignore it**

- Treat associated conditions
  - Hypertension
  - Hyperlipidemia
  - Metabolic syndrome

- Dietary modifications are essential
Normal Uric Acid Production and Excretion

Where Does Urate Come From?

About two-thirds of uric acid is generated endogenously by the body, while one-third comes from purines in the diet.

No Uricase in Humans and Higher Primates

Most Cases of Primary Hyperuricemia are Caused by Inefficient Renal Excretion

Primary hyperuricemia caused by inefficient renal excretion of urate: 80%1–3

Possible genetic causes:
- Missense mutations in genes encoding NPT1 and NPT4
- Gain-of-function mutations in transport-related proteins (e.g. PDZK1, CARMIL, NHERF-1) which promote URAT1 reabsorption6

Primary hyperuricemia caused by apparent overproduction of urate: 20%1,2,4

Known causes include mutations in enzymes leading to increased purine synthesis (e.g. partial HPRT deficiency; Kelley-Seegmiller syndrome)7

The contribution of inefficient intestinal excretion of urate to rates of primary hyperuricemia is not known. HPRT=hyoxanthine-guanine phosphoribosyltransferase; NHERF-1=sodium–hydrogen antiporter 3 regulator 1; NPT1/4=sodium-dependent phosphate transporter type 1/4; URAT=urate transporter.

Gout Risk Factors

- Advancing age
- Male gender
- Family history of gout
- Obesity
- Certain drugs: diuretics, low dose aspirin, cyclosporin
- Alcohol, especially beer and binge drinking
- Lead toxicity
- Organ transplants
- Thyroid problems
- Other serious illness

Contribution of Diet and Lifestyle to Hyperuricemia

- Normally, only around one third of our source of purines is dietary\(^1\)

- A diet rich in purines only has a small and transient increase on sUA (1–2 mg/dL)\(^1\)

- Obesity is also a lifestyle risk factor associated with hyperuricemia\(^2\)
  - Increases production and reduces renal excretion of urate\(^1–3\)

sUA=serum urate.

Crystal Formation Is a Major Step in Development of Gout

- MSU crystals form at an sUA level of 6.8 mg/dL at 37°C (in vitro)\textsuperscript{1–5}

MSU=monosodium urate; sUA=serum urate.
MSU Crystals Can Deposit in Joints Anywhere in the Body

- Olecranon bursa
- Elbow
- Wrists
- Fingers
- Knee
- Ankle
- Subtalar
- Midfoot
- First MTP joint

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Less common

More common

First MTP joint
- Affected in ~50% of first flares
- Eventually involved in 90% of patients

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Prior to Any Clinical Manifestations of Gout, MSU Crystal Deposits Can Build Up$^1,2$

MSU = monosodium urate.

In Addition to Joints, MSU Crystals May Deposit in Soft Tissues, Such as Kidney and Eye

Chronic urate nephropathy occurs with the deposition of MSU crystals in the kidney¹

Conjunctival gouty tophi have been reported²

Ophthalmologic examination revealing multiple chalky deposits on the corneal stroma of a patient with longstanding untreated gout (arrow). Polarized light microscopy examination of a scraping from a deposit revealed typical MSU crystals³

MSU=monosodium urate.
Gout Flares Occur When Crystals Trigger an Acute Inflammatory Response

- Flares occur without warning and may:
  - Produce extreme pain
  - Last hours to weeks
  - Limit mobility

- Acute flares may be triggered by fluctuations in sUA levels, which can mobilize crystals

- Crystals released into the joint space undergo phagocytosis

- Phagocytosis can initiate a proinflammatory response, resulting in gout flares

- Over time, flares may occur more often

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The Incidence of the First Gout Flare Increases as sUA Increases

In the Normative Aging Study of 2,046 initially healthy men, it was shown that the incidence of the first gout flare increased as the most recent sUA recorded increased.

<table>
<thead>
<tr>
<th>sUA (mg/dL)</th>
<th>Person–years of observation</th>
<th>Number of first gout flares</th>
<th>Incidence rate (per 1000 person–years)</th>
<th>5-year cumulative incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤6.0</td>
<td>12,456</td>
<td>10</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>6.0–6.9</td>
<td>10,346</td>
<td>13</td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>7.0–7.9</td>
<td>5,154</td>
<td>21</td>
<td>4.1</td>
<td>2.0</td>
</tr>
<tr>
<td>8.0–8.9</td>
<td>1,660</td>
<td>14</td>
<td>8.4</td>
<td>4.1</td>
</tr>
<tr>
<td>9.0–9.9</td>
<td>417</td>
<td>18</td>
<td>43.2</td>
<td>19.8</td>
</tr>
<tr>
<td>≥10.0</td>
<td>114</td>
<td>8</td>
<td>70.2</td>
<td>30.5</td>
</tr>
</tbody>
</table>

sUA=serum urate.
Persistence of High sUA is Associated with an Increased Risk of Recurrent Flares

*Average sUA was calculated over 3 years for patients who received treatment. A retrospective study of 267 patients who attended the Institute of Rheumatology, Tokyo Women’s Medical University for gout treatment. Patients experienced ≥1 flare before their first visit and attended the clinic for >1 year.

Urate Crystals Continue to Deposit Between Flares During Intercritical Periods\textsuperscript{1,2}

Resolution of pain in between flares

Constant joint pain

Tissue deposition of MSU crystals\textsuperscript{2}

\begin{itemize}
\item **Asymptomatic hyperuricemia**: During this period, urate continues to deposit in joints and soft tissues.
\item **Gout flares**: During this period, urate crystals are still present in the synovial fluid and soft tissues and may be accumulating.
\item **Advanced tophaceous gout**: Tissue stores of urate continue to increase if hyperuricemia persists at biologically significant levels (>6.8 mg/dL).
\end{itemize}

Development of Tophi Increases with Time and Severity of Hyperuricemia

A retrospective analysis of 1165 patients with gout before appropriate drug therapy. sUA=serum urate; ULT=urate-lowering therapy.

Development of Tophi can Lead to Joint Damage, Bone Erosion and Progressive Disability\textsuperscript{1–4}

\begin{itemize}
\item Tophaceous gout of the hand showing numerous subcutaneous tophi
\item X-ray of hand with tophaceous gout showing bone erosion of index finger (white arrow)
\end{itemize}

\textit{Image s courtesy of Dr Fernando Perez-Ruiz, Rheumatology Department, Cruces University Hospital, Barakaldo, Spain}


Summary: Sustained Hyperuricemia Underlies the Progression of Gout

<table>
<thead>
<tr>
<th>Asymptomatic period</th>
<th>Acute clinical manifestations</th>
<th>Chronic clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated sUA with no clinical gout</td>
<td>Recurrent acute gout flares</td>
<td>Short intervals between flares</td>
</tr>
<tr>
<td>Silent tissue deposition begins</td>
<td>Prolonged intervals between flares</td>
<td>Chronic synovitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visible tophi</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Joint destruction</td>
</tr>
</tbody>
</table>

sUA=serum urate.

Comorbidities Are Frequently Observed in Individuals With Gout

- The most frequent comorbidities observed in US patients with gout were hypertension, CKD stage ≥2, obesity and diabetes.

Figure adapted from Zhu Y, et al. (2012) Showing the calculated prevalence and population estimates from participants in the NHANES 2007–2008 (n=5707) of comorbidities in those with and without gout. CKD=chronic kidney disease; NHANES=National Health and Nutrition Examination Survey.

Risk of CHD and Myocardial Infarction Increases as sUA Rises

- A population-based cohort study with 10 years of follow-up showed that participants with the highest levels of sUA had the greatest risk of CHD and myocardial infarction.

<table>
<thead>
<tr>
<th>sUA (mg/dL)</th>
<th>HR (95% CI)</th>
<th>CHD (n=515)</th>
<th>Myocardial infarction (n=194)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–4.20</td>
<td>1.0 (reference)</td>
<td>1.0 (reference)</td>
<td></td>
</tr>
<tr>
<td>4.21–4.89</td>
<td>1.01 (0.73–1.40)</td>
<td>1.01 (0.57–1.79)</td>
<td></td>
</tr>
<tr>
<td>4.90–5.48</td>
<td>1.40 (1.03–1.90)</td>
<td>1.91 (1.15–3.19)</td>
<td></td>
</tr>
<tr>
<td>5.49–6.39</td>
<td>1.32 (0.97–1.79)</td>
<td>1.72 (1.03–2.87)</td>
<td></td>
</tr>
<tr>
<td>≥6.40</td>
<td>1.68 (1.24–2.27)</td>
<td>1.87 (1.12–3.13)</td>
<td></td>
</tr>
</tbody>
</table>

CHD=coronary heart disease; CI=confidence interval; HR=hazard ratio; sUA=serum urate.
CKD Associated With Gout

- 71% of US patients with gout have stage 2 or higher CKD\(^1\)
- Annual reduction in GFR
  - Healthy adults
    - 0.8-1.3 mL/min
  - Untreated hyperuricemic adults
    - 2.5 mL/min/1.73 m\(^2\)

Joint Aspiration and Synovial Fluid Analysis

Best Measure for Definitive Diagnosis of Gout

- Urate crystals identified by
  - Strong negative birefringence
  - Needle and rod shapes
- Infection and crystals can be seen together
- Helps rule out other causes
  - eg, RA, pseudogout

Gold Standard: Compensated Polarized Light Microscopy

RA, rheumatoid arthritis.
Joint Aspiration

*Ideal vs Practical*

**Ideal**
Definitive diagnosis of gout achieved by joint aspiration in each patient

**Common Practice**
PCPs and patients reluctant to aspirate inflamed joints
Performed in approximately 10% of gout cases

**ACTION ITEM:**
If presumptive diagnosis of gout criteria is unclear, aspirate the joint, particularly if septic arthritis is possible

Imaging Urate Crystal Deposits and Tophaceous Gout

Plain X-ray: Insensitive in early disease
Ultrasound: Sensitive in early disease
CT Scan: Sensitive, but expensive
MRI: Sensitive, but expensive

CT, computed tomography; MRI, magnetic resonance imaging.
Differential Diagnosis

- Septic arthritis
- Pseudogout
- Cellulitis
- Osteoarthritis of first MTP joint or nodal osteoarthritis of small hand joints
- RA (vs chronic tophaceous gout)
- Psoriatic arthritis, spondyloarthropathy
- Lyme disease
  - Limited flares of painful oligoarthritis, typically involving the knee

Treating Gout Flares: Key Points

- *When you start therapy is more important than which agent you use (ACR recommends ≤ 24 hours)*

- Select agent considering patient comorbidities

- The sooner treatment is initiated after symptoms begin, the faster it will work

- When taken at the earliest hint of a flare, attacks may be aborted with one dose

2012 ACR Gout Guidelines
Pharmacologic Therapy for Acute Flares

Assess Severity

Mild/Moderate Pain or 1-2 Small or Large Joints

Monotherapy

NSAIDs
Most can be used at maximum approved doses
Monitor for toxicities

Systemic Corticosteroids
Prednisone or prednisolone
>0.5 mg/kg/d for 5-10 days

Colchicine
1.2 mg initially and 0.6 mg 1 hour later (fewer side effects than higher doses)

Combination therapy
- Colchicine + NSAID
- Oral corticosteroid + colchicine
- Intra-articular steroids with all other modalities

Polyarticular or Multiple Large Joints with Severe Pain

- Supplement with topical ice as needed
- Initiate therapy within 24 h of acute gout flare onset
- Continue pharmacologic urate-lowering therapy during acute attacks


COX-2, cyclooxygenase-2; NSAID, nonsteroidal anti-inflammatory drug.
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Pharmacologic Therapy for Acute Flares (cont’d)

Inadequate Response defined as <20% in pain within 24 h or <50% improvement ≥24 h.


Patient Education
- Diet and lifestyle triggers
- Prompt self-treatment of subsequent attacks

Urate-Lowering Therapy
- Consider indications
- Adjust ongoing regimen

Alternate Monotherapy
- Consider alternative diagnosis

Combination Add-on Therapy
- Successful Outcome

Inadequate Response

Successful Outcome

Treatment Outcome

Off-Label Therapies in Development

Inadequate response defined as <20% in pain within 24 h or <50% improvement ≥24 h. Khanna D, et al. Arthritis Care Res (Hoboken). 2012;64(10):1447-1461.
Flare Management: NSAIDS

- Take as soon as symptoms begin, such as
  - Ibuprofen*
  - Naproxen*
  - Indomethacin*
- Determine the correct dose with the patient - usually needs max dose
- Should not be used in:\(^1\)
  - Gastric bleeding
  - Renal failure
  - Heart failure
- Gastric AE’s\(^2\)
  - Proton pump inhibitor may be given


*Refer to package insert for adverse events and safety data
Flare Management: Colchicine

- Oral colchicine used in two situations:
  1. Acute Flare
     - Dose adjustment in CKD and/or drug interaction, unless lack of tolerance or medical contraindication
  2. Flare Prophylaxis
     - Colchicine 0.6 daily or bid for 3-6 months or longer

Note: Chronic use of colchicine among gout patients linked with a decreased risk of myocardial infarction


CKD, chronic kidney disease
ACR 2012 Gout Guidelines

After the Initial Acute Attack...

- Counsel on factors that can precipitate attack
- Implement diet and lifestyle changes to prevent flares
- Consider secondary causes of hyperuricemia
- Eliminate nonessential medications that induce hyperuricemia
- Evaluate gout disease burden
  - Palpable tophi
  - Frequency and severity of acute and chronic symptoms
- Assess and encourage adherence with medications
  - Review dosing schedule, instructions, potential AEs

### 2012 ACR Gout Guidelines

**General Health, Diet, and Lifestyle Recommendations**

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

<table>
<thead>
<tr>
<th>Avoid</th>
<th>Limit</th>
<th>Encourage</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Organ meats high in purine content (eg, sweetbreads, liver, kidney)</td>
<td>- Beef, lamb, pork</td>
<td>- Low-fat or non-fat dairy products</td>
</tr>
<tr>
<td>- High fructose corn syrup-sweetened sodas, other beverages, or foods</td>
<td>- Seafood with high purines (eg, shellfish)</td>
<td>- Vegetables</td>
</tr>
<tr>
<td>- Alcohol overuse (&gt;2 drink/day for men or &gt;1 drink/day for women)</td>
<td>- Serving of naturally sweet fruit juices</td>
<td></td>
</tr>
<tr>
<td>- Any alcohol use during periods of frequent attacks, or in poorly controlled advanced gout</td>
<td>- Table sugar, sweet beverages, and desserts</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Table salt, including in sauces</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Alcohol (particularly beer, but also wine and spirits) in all patients</td>
<td></td>
</tr>
</tbody>
</table>
2012 ACR Gout Guidelines

Initiating Urate-Lowering Therapy

- Do not start urate-lowering therapy during an attack unless good anti-inflammatory treatment and prophylaxis are in place
  - Fluxes in urate levels can precipitate acute flares
- Increased surveillance necessary for gout determinants
- Monitor regularly until serum urate target is achieved
  - Incidence of flares and serum urate levels decline over time with effective treatment
- Timing is important
  - Adherence to urate-lowering therapy is often poor, especially in the first year

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2012 ACR Gout Guidelines
Current Recommendations for Urate-Lowering Therapy

Treat to individualized serum urate targets

- The usual serum urate target is <6 mg/dL
- Serum urate levels <5 mg/dL may be needed to improve gout signs and symptoms

First Line Agent
Xanthine Oxidase Inhibitor
- Allopurinol

If ≥1 xanthine oxidase inhibitor is contraindicated or not tolerated
- Probenecid

Alternative First-Line Agent
- Febuxostat

Acute Gout Prophylaxis
Initiate concomitant pharmacologic gout attack prophylaxis

2012 ACR Gout Guidelines
Allopurinol as First Line Urate-Lowering Therapy

- Effective in uric acid overproducers and underexcretors
- Published efficacy/safety data for doses ≥300 mg limited
- Maximum FDA-approved dose, 800 mg/d
  - Reduced in CKD
- Start at ≤100 mg/d (50 mg/d with severe CKD)
  - Gradual dose escalation every 2 to 5 weeks to reduce flare risk
  - BID dosing when dose is >300 mg to avoid GI effects
- Check renal and liver function before and during treatment

FDA, Food and Drug Administration; PCR, polymerase chain reaction.
Allopurinol
Limitations as Urate-Lowering Therapy

- Intolerance in 5%-10% (eg, liver function, GI, CNS)
- Pruritic rash in ~2%
- Major allopurinol hypersensitivity syndrome
  - Incidence 0.1%-0.4% (~25% mortality)
  - Usually in first months of therapy
  - More common with CKD, thiazides, HLA-B*5801
    - Consider pharmacogenetic HLA-B*5801 PCR testing in high-risk populations (Han Chinese, Thai, Koreans)

CNS, central nervous system; PCR, polymerase chain reaction.
Allopurinol Dosing
Current Usage vs Suggested Needs

Mean dose required to achieve urate targets (<6.0 mg/dL) in small study of 49 patients with gout.

Urate-Lowering Therapy

Febuxostat

- Selective inhibitor of xanthine oxidase with nonpurine backbone
- Dose: 40 mg/d starting dose, labeled use up to 80 mg/d
  - ACR allows doses up to 120 mg (approved in Europe)
- Advantages
  - More selective than allopurinol
  - Lower renal excretion vs allopurinol active metabolite
  - No dose adjustment with mild/moderate renal or hepatic impairment
- More expensive but well-tolerated alternative to allopurinol

WARNING: CARDIOVASCULAR DEATH
See full prescribing information for complete boxed warning.

- Gout patients with established cardiovascular (CV) disease treated with ULORIC had a higher rate of CV death compared to those treated with allopurinol in a CV outcomes study. (5.1)

- Consider the risks and benefits of ULORIC when deciding to prescribe or continue patients on ULORIC. ULORIC should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable. (1)
Urate-Lowering Therapy

**Uricosurics**

- Increase urate excretion by inhibiting urate reabsorption in the kidney
- Probenecid – only FDA-approved uricosuric
  - Alternative in those intolerant to xanthine oxidase inhibitors
  - Not recommended in persons with history of urolithiasis
    - Increases urolithiasis risk, especially with acidic urine pH
    - Not recommended if CrCl <50 mL/min
- Losartan, atorvastatin, and fenofibrate
  - Less potent
  - Off label

CrCl, creatinine clearance.
Urate-Lowering Therapy for Refractory Disease

**Pegloticase**

- Drug antigenicity may cause loss of drug effect and infusion reactions
- Stop oral urate-lowering therapy to avoid masking antibody-mediated loss of urate-lowering effect by pegloticase

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Positive response defined as a plasma urate levels <6.0 mg/dL for ≥80% of the time during months 3 and 6.

N=85 patients receiving biweekly intravenous pegloticase and 43 patients receiving placebo at baseline.

Urate-Lowering Therapy
Emerging Options in Development

- Lesinurad (only available in Europe)
  - Selective uric acid reabsorption inhibitor that inhibits URAT1 and OAT4 transporters in the renal tubule
  - Available in 200 mg dose, only as add on to allopurinol or febuxistat
  - Approved but as of 2/1/19 no longer commercially available in the US

- Ulodesine
  - Purine nucleoside phosphorylase inhibitor
  - Blocks production of uric acid higher in the purine catabolic pathway than xanthine oxidase inhibition

- Arhalofenate
  - Dual-acting anti-inflammatory and urate-lowering therapy
  - Oral IL-1β inhibitor combined with uricosuric effects

Initiating Urate-Lowering Therapy

Flare Risk Without Prophylactic Coverage

- Patients prescribed a prophylactic anti-inflammatory regimen from baseline to Week 8

N=762 patients with gout.
Gout Flare Risk Increases With ULT

- Expect gout flares with all ULT strategies, especially in first 6 months of treatment
  - *Remain on ULT during flares*
  - Flares indicate effective ULT due to tophus remodeling

- Manage flares
  - Initiate prophylaxis 1-2 weeks before starting ULT

*Important: unexpected flares decrease compliance with ULT - educate patient!*

2012 ACR Gout Guidelines
*Gout Flare Prophylaxis*

**Initiate with or just before initiating pharmacologic urate-lowering therapy**
- **First-line:** Low-dose colchicine (0.6 mg once or twice daily) *OR* Low-dose NSAID (with PPI where indicated)
- **Second-line:** Low-dose prednisone or prednisolone (≤10 mg/d)

**Evaluate gout symptoms with urate-lowering therapy**
- **Gout Signs/Symptoms:** Continue pharmacologic anti-inflammatory prophylaxis
- **No Gout Signs/Symptoms:** Evaluate gout symptoms with urate-lowering therapy

**Treat for the LONGEST Period Among the Following**
- At least 6 months
- 3 months after achieving target serum urate level with no tophi
- 6 months after achieving target serum urate level with ≥1 tophi

**ACTION ITEM:**
Prescribe prophylactic anti-inflammatory therapy for ≥6 months when initiating a pharmacologic urate-lowering regimen.

PPI, proton pump inhibitor.
Gout Flare Prophylaxis With Colchicine

*Flare Prevention After Starting Allopurinol*

- Colchicine dose: 0.6 mg twice daily for ~6 months (many switched dose to 0.6 mg once daily)

N=43 patients starting allopurinol for crystal-proven chronic gouty arthritis.
2012 ACR Gout Guidelines

Long-term Management

Treat to target
Serum urate level achieved?

YES

▪ Continue gout attack prophylaxis for ongoing gout symptoms and/or signs (≥1 tophus on physical exam)
▪ Regularly monitor serum urate and assess for treatment AEs
▪ After palpable tophi and all acute and chronic symptoms have resolved, continue all measures (including pharmacologic urate-lowering therapy) to maintain serum urate at target indefinitely

NO

▪ Increase intensity of urate-lowering therapy
▪ Re-evaluate serum urate

Summary

- Gout is clinical diagnosis
  - If presumptive diagnosis is unclear, aspirate the joint
  - Use ultrasound
- Use appropriate acute flare treatment with either NSAID, or corticosteroid, or colchicine
- Initiate pharmacologic urate-lowering therapy in all patients with tophus, multiple attacks/year, CKD ≥stage 2, or previous urolithiasis
- Prescribe prophylactic anti-inflammatory therapy for at least 6 months when initiating a pharmacologic urate-lowering regimen
- Treat to target: SUA < 6 mg/dl (<5 mg/dl in tophaceous gout, and difficult treat gout)
- Follow with biannual assessment with lab tests