Recommendations for the Management of Gout and Hyperuricemia
This CME activity is intended for practicing physicians, and other health care providers who may treat patients who have Gout and Hyperuricemia.

There is no fee for participation in this CME activity.

This program is made possible through an educational grant from Savient Pharmaceuticals, Inc. and URL Pharma, Inc.
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of UHS-PEP of Virginia Commonwealth University Health System and Miller Professional Group. UHS-PEP is accredited by the ACCME to provide continuing medical education for physicians.

VCU designates this educational activity for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.
Disclosure of Significant Relationships with Relevant Commercial Interests

Neither *VCU* nor Miller Professional Group has any commercial interests relevant to the content of this activity. The content of this CME activity will not contain discussion of off-label uses. Please consult the product prescribing information for full disclosure of labeled uses.
These members of the faculty and/or VCU UHS-PEP faculty and staff disclose the following relevant relationships to commercial interests:

- Thomas Adamson, III, MD is a member of the Speaker’s Bureau for Warner Chilcott and Pfizer; and participated in a one-time speaking even for Interpace BioPharma.
- Herb Baraf, MD is a member of the Speaker’s Bureau for Savient and Takeda and is an Investigator for Savient, Takeda, Ardea, Metabollix and Regeneron; and is a Consultant for Savient.
- Howard Blumstein, MD is a member of the Speaker’s Bureau for Abbott, UCB, Warner Chilcott and Genentech.
- Alan Brown, MD is a member of the Speaker’s Bureau for Takeda.
- Paul Doghramji, MD is a member of the Speaker’s Bureau and a Consultant for URL.
- N. Lawrence Edwards, MD is a Consultant for Takeda, Savient, Novartis, Ardea and Regeneron.
- Alan Epstein, MD is a member of the Speaker’s Bureau for Takeda and HGS.
- Madelaine Feldman, MD has no relationships to report.
- Germano Guadagnoli, MD is a member of the Speaker’s Bureau for Pfizer, Amgen, Takeda, URL and Savient.
- Max Hamburger, MD is a member of the Speaker’s Bureau for Amgen, BMS, Genentech and UCB; is a Consultant for Amgen and BMS; and has obtained Med Ed grants on behalf of 3rd parties from Abbott, Amgen, BMS, Centocor, Genentech and UCB. Miller Professional Group (MPG), a medical education and communications company, owned by a family member; has been the recipient of CME grants from Abbott, Amgen, BMS, Centocor, Crescendo, Genentech, Biogen Idec, Roche, and URL.
- Joseph Huffstutter, MD is a member of the Speaker’s Bureau for Takeda, HGSI and Savient.
- Richard Jimenez, MD is a member of the Speaker’s Bureau for Takeda.
- Joseph Lieberman III, MD has no relationships to report.
- Kenneth Miller, MD has no relationships to report.
- Eric Mizuno, MD has no relationships to report.
DISCLOSURES of FACULTY CONFLICTS OF INTEREST

- Alan Morton, DO is a member of the Speaker’s Bureau for Pfizer, Amgen, UCB, URL, BMS, Takeda, Genentech, Abbott, Warner Lambert and Savient; and is a Consultant for Pfizer, Amgen, URL, BMS, Savient and Novartis.
- David Mount, MD has no relationships to report.
- Richard Pope, PA-C is a member of the Speaker’s Bureau for Takeda and URL.
- Gregory Schimizzi, MD has no relationships to report.
- Paul Schulman, MD has no relationships to report.
- Katy Setoodeh, MD is a member of the Speaker’s Bureau for Amgen and HGS.
- Evan Siegel, MD is a member of the Speaker’s Bureau for Amgen and Abbott.
- John Skosey, MD is a Stockholder in Amgen and TheraTest Laboratories and is a Director of TheraTest Laboratories.
- Michael Weitz, MD is a member of the Speaker’s Bureau for Savient.

All conflicts of interest due to reported relationships above have been resolved according to VCU’s Policy on Conflict of Interest and the Standards for Commercial Support of the ACCME.

All presenting faculty affirm that they will employ the best available evidence from all sources to support any clinical recommendations made in their presentations.
After Participating in the Educational Activity, Attendees should be able to:

• Describe the patho-physiology of hyperuricemia and gout

• Describe recent advances in the understanding of the epidemiology of gout and hyperuricemia, and the relationship between hyperuricemia, risk factors and co-morbidities

• Apply recommended guidelines for correctly diagnosing gout and hyperuricemia

• Manage gout and hyperuricemia in accordance with recommended guidelines and incorporate data on efficacy and safety
  
  – Manage the acute attack
  – Implement prophylaxis and urate lowering therapy
  – Management of chronic hyperuricemia
  – Manage the refractory or challenging patient
2011 Recommendations for the Diagnosis and Management of Gout and Hyperuricemia

Max Hamburger, MD
Herbert S. B. Baraf, MD
Thomas C. Adisman III, MD, FACP, CPE
Jan Basile, MD
Lewis Bass, DO, FACOFP
Brent Cole, MD
Paul P. Doghramji, MD
Germano A. Guadagnoli, MD
Frances Hamburger, PhD
Regine Harford, MS, MSTPC
Joseph A. Lieberman III, MD, MPH
David R. Mandel, MD
Didier A. Mandelbrot, MD
Bonny P. McClain, MS, DC
Eric Mizuno, MD
Allan H. Morton, DO
David B. Mount, MD
Richard S. Pope, MPAS, PA-C, DFAAPA
Kenneth G. Rosenthal, MD, PC
Katy Setoodeh, MD, FACP
John L. Skosney, MD, PhD, FACP, FACC
N. Lawrence Edwards, MD, FACP, FACC

Abstract: Gout is a major health problem in the United States; it affects 8.3 million people, which is approximately 4% of the adult population. Gout is most often diagnosed and managed in primary care physician practices. Primary care physicians have a significant opportunity to diagnose and manage patients with gout and improve patient outcomes. Following publication of the 2006 European League Against Rheumatism (EULAR) gout guidelines, significant evidence on gout has accumulated and new treatments for patients with gout have become available. It is the objective of these 2011 recommendations for the diagnosis and management of gout and hyperuricemia to update the 2006 EULAR guidelines, paying special attention to the needs of primary care physicians, who manage most patients with gout. The revised 2011 recommendations are based on the Grading of Recommendations Assessment, Development, and Evaluation approach as an evidence-based strategy for rating quality of evidence and grading strength of recommendation in clinical practice. A total of 26 key recommendations for diagnosis (n = 10) and management (n = 16) were evaluated. Presence of tophi (proven or suspected) and response to colchicine had the highest clinical diagnostic value (likelihood ratio [LR], 15.56 [95% CI, 2.11–114.71] and LR, 4.13 [95% CI, 1.16–16.16], respectively). The key aspect of effective management of an acute gout attack is initiation of treatment within hours of onset of first symptoms. Low-dose colchicine is better tolerated than and is as effective as high-dose colchicine (number needed to treat [NNT], 5 [95% CI, 3–13] and NNT, 6 [95% CI, 3–72], respectively). For urate-lowering therapy, allopurinol in combination with probenecid was shown to be more effective than either agent alone (effect size [ES], 5.51 for combination; ES, 4.46 for probenecid; and ES, 2.80 for allopurinol). Febuxostat, also a xanthine oxidase inhibitor, has a slightly different mechanism of action and can be prescribed at unchanged doses for patients with mild-to-moderate renal or hepatic impairment. Febuxostat 40 mg versus 80 mg (NNT, 6 [95% CI, 4–11]) and 120 mg (NNT, 6 [95% CI, 3–26]) both demonstrated long-term efficacy. The target of urate-lowering therapy should be a serum uric acid level of ≤ 6 mg/dL. For patients with refractory and tophaceous gout, intravenous pegloticase is a new treatment option.

Keywords: gout; hyperuricemia; guideline recommendations; rheumatology

Introduction
Gout is a major health problem in the United States; it affects 8.3 million people, which is approximately 4% of the adult population. Although gout is well understood and has good therapeutic options, it tends to be poorly managed, with insufficient patient evaluation, inappropriate use of traditional and new medications, and low patient compliance. Because gout is most often diagnosed and managed in primary care physician (PCP) practices, PCPs have a significant opportunity to ensure that more patients diagnosed with gout receive optimized, state-of-the-art care.
A multidisciplinary team with members specializing in rheumatology, nephrology, cardiology, primary care, and allied health reviewed the diagnostic and management recommendations published by EULAR in 2006.\textsuperscript{11, 12}

The EULAR evidence hierarchy for diagnosis and management of gout was based primarily on study design.

The revised recommendations are based on the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach\textsuperscript{13} as an evidence-based strategy for rating quality of evidence and grading the strength of recommendations formulated for use in clinical practice.
Strength of Recommendation

- Strength-of-recommendation scores express expert experience and consensus.

- Each team member rated the strength of each agreed-on recommendation on 2 scales:
  - a categorical scale (as fully, strongly, moderately, weakly, or not recommended)
  - a visual analog scale (VAS) ranging from 60 (weak recommendation) to 100 (strong recommendation).

- Based on categorical data, the percentage of strongly and fully recommended scores was calculated for each recommendation.

- Analysis of continuous data resulted in a mean VAS score with 95% confidence intervals for each recommendation.
The numbered recommendations in this presentation were taken with permission from:

2011 Recommendations for the Diagnosis and Management of Gout and Hyperuricemia
Postgraduate Medicine
Volume 123 Issue 6 Supplement 1
Hamburger et al
Sir Thomas Sydenham: Description of Acute Gout: 1848

The victim goes to bed and sleeps in good health. About two o'clock in the morning he is awakened by a severe pain in the great toe; more rarely in the heel, ankle or instep. This pain is like that of a dislocation. ... Then it is a violent stretching and tearing of the ligaments. ... now it is a gnawing pain and now a pressure and tightening.

... He cannot bear the weight of bedclothes nor the jar of a person walking in the room. The night is passed in torture, and perpetual change of posture; the tossing about of the body being as incessant as the pain of the tortured joint.

A Renaissance for Uric Acid?

- Increasing incidence of gout

- Mapping/characterization of genes associated with hereditary hyperuricemic nephropathy, uric acid stones, hyperuricemia, and gout

- Evolving associations with hyperuricemia:
  - Kidney stones
  - Insulin resistance syndrome / metabolic syndrome
  - Hypertension, renal disease
  - Prognosis of vascular disease, heart failure, stroke
  - Protection from Parkinson’s, multiple sclerosis, AD
Gout

- Gout: Acute arthritis, typically very severe
- Most common form of inflammatory joint disease.

Disease Process

- Urate: End product of purine metabolism
- Blood level of urate > physiologic limit of solubility (6.8mg/dL): Tissue crystallization
- Sodium in tissues: Conversion of urate to monosodium urate (MSU)
- Inflammatory response to the presence of MSU crystals: Acute Gout

## Gout - a Progressive and Disabling Disease

One Chronic Disease - 4 Stages

<table>
<thead>
<tr>
<th>Asymptomatic hyperuricemia&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Gout&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>sUA ≥ 7 mg/dl</td>
<td>Acute flares</td>
</tr>
<tr>
<td>~32 million in US</td>
<td>Intercritical Period</td>
</tr>
<tr>
<td>Progression to gout: 20 – 30%</td>
<td>Persistent or Progressive gout</td>
</tr>
<tr>
<td>Necessary but not sufficient for gout</td>
<td>Chronic Arthropathy and Tophi</td>
</tr>
<tr>
<td></td>
<td>~5 million</td>
</tr>
<tr>
<td></td>
<td>Increasing frequency and duration of attacks</td>
</tr>
<tr>
<td></td>
<td>Polyarticular presentation</td>
</tr>
<tr>
<td></td>
<td>Chronic synovitis</td>
</tr>
<tr>
<td></td>
<td>Visible tophi</td>
</tr>
</tbody>
</table>

### Disease Progression

Pathogenesis of Hyperuricemia

Sources and distribution of uric acid in an adult man
Endogenous purine synthesis

Tissue nucleic acids

Dietary purines

600 mg

100 mg

Miscible urate pool

2000 mg

Purine Sources

Total Body Uric Acid Pool

Purine Elimination

Renal excretion

Intestinal uricolyis

300 mg

300 mg

Insoluble urate pool

1 to >100 grams
Consequences of Expanded Urate Pools

Miscible urate pool

2000 mg

Insoluble urate pool

1 to >40 grams

Asymptomatic hyperuricemia

Hypertension, kidney & heart disease

Renal Manifestations

Gouty arthritis

Urate tophi
Diagnostic Recommendations
Diagnostic Recommendation: Assess for Risk Factors

Risk factors for gout should be assessed, including features of the metabolic syndrome (obesity, hyperglycemia, hyperlipidemia, and hypertension), chronic kidney disease (CKD), medications, family history, and lifestyle. (#10)
### Risk Factors & Co-Morbid Conditions

#### Risk Factors

**Modifiable**
- Obesity
- Serum urate
- High-fructose corn syrup
- Purine-rich diets
  - Meats (organ meats), Seafood
- Alcohol consumption
- Medications
  - Diuretics, Low-dose aspirin, Cyclosporine, Ethambutol

**Non-modifiable**
- Age
- Gender
  - Male
  - Postmenopausal females

#### Co-Morbid Conditions

**Metabolic Syndrome**
- Hypertension
- Diabetes Mellitus
- Obesity

**Cardiovascular Disease**
- Myocardial Infarction
- Peripheral artery disease
- Congestive heart failure

**Impaired Renal Function**

---

9. KRYSTEXXA™ (pegloticase) for intravenous infusion, Briefing Document for Arthritis Advisory Committee.
Risk Factors for Development of Gout: Diet

- **Study Results:**
  - Risk from caffeine: 5+ caffeinated beverages/day ↓ risk of gout
  - Risk from alcohol intake: Beer > liquor > wine
  - High meat consumption: ↑ risk of gout
  - High seafood consumption: ↑ risk of gout
  - High dairy consumption: ↓ risk of gout
  - “Low-purine diet” results in modest 1-mg reduction in baseline serum uric acid
  - High consumption of purine-rich vegetables or total protein: no association

Dietary Purine Intake and Serum Uric Acid Levels

- Severe reduction in dietary purine intake can accomplish no more than a 1 mg/dl decrease in serum uric acid.

- Exception: Reduction of dietary fructose
  - Only carbohydrate that influences purine metabolism
  - Implicated in insulin resistance, metabolic syndrome and obesity
  - An apple a day? Ingestion of 5 apples=35% increase in serum uric acid within 6 hours

Medications Affecting Urate Excretion

- Thiazides and loop diuretics
- Low dose aspirin
- Cyclosporin A
- Anti-tuberculous medications
  - pyrazinamide and ethambutol
- Niacin
- PTH therapy
Hyperuricemia: Cardiovascular Risk Factor?

• Chronic inflammation associated with chronic gout

• Stronger risk factor in those already at high risk for cardiovascular disease


Acute Gout

- Acute arthritis, typically monoarticular and very severe
  - Inflammatory response to the presence of monosodium urate (MSU) crystals
  - Urate: end product of purine metabolism

- Most common form of inflammatory joint disease in men*

- Crystallization occurs when the blood level of urate > physiologic limit of solubility: 6.8mg/dl

Diagnostic Recommendation: Know the Clinical Picture of Gout

In acute monoarticular attacks of the lower extremities, the rapid development of severe pain, swelling, and tenderness that reaches its maximum within 6 to 12 hours, especially with overlying erythema, is highly suggestive of crystal inflammation, though not specific for gout. (#1)
Diagnostic Recommendation: Normal Serum Uric Acid Levels Don’t Confirm or Exclude Gout

While being the most important risk factor for gout, serum uric acid (SUA) levels do not confirm or exclude gout, as many people with hyperuricemia do not develop gout, and SUA levels may be normal during acute attacks. (#3)

Elevated IL-6 levels are uricosuric, contributing to a drop in SUA during acute attack.
Common Sites of Acute Gout Attacks

Gout can occur in bursae, tendons, and joints.

1st MTP (eventually affected in ~90% of individuals with gout)

- Olecranon Bursa
- Elbow
- Wrist
- Fingers
- Knee
- Ankle
- Subtalar
- Midfoot
Precipitating Factors

- Trauma, including surgery
- Diuretics-other medications
- Dietary indiscretion
- Dehydration
- Low temperature of affected limb
- Alcohol: Beer > Liquor > Wine
- Systemic illness
- Dehydration or volume depletion for any reason
Special Considerations for Diagnosing Gout

• Look for gout, even if
  • Serum uric acid levels are normal
  • The symptoms present in a woman
  • The attack is polyarticular and chronic
  • The involved joint is atypical

• Don’t treat to diagnose:
  • Other types of acute arthritis may also respond to colchicine
Differential Diagnosis of Gout

- Septic Joint
- Trauma, Hemarthrosis
- Pseudogout (CPPD/chondrocalcinosis)
- Hyperuricemia unrelated to joint pain
  - Monoarticular onset of rheumatoid arthritis
  - Bursitis, tendonosis
Gout and sepsis may coexist; therefore, when septic arthritis is suspected, Gram staining and culture of synovial fluid should still be performed, even if MSU crystals are identified. (#6)
Diagnostic Recommendation: A Clinical Diagnosis Alone May Suffice

- Although only the demonstration of MSU crystals in synovial fluid or tophus aspirates constitutes a definite diagnosis of gout......

- a clinical diagnosis alone is a reasonable alternative in patients with the typical presentation of gout. (#2)
Diagnostic Recommendation: Crystal Identification May Establish Diagnosis

When the diagnosis is in doubt, identification of MSU crystals from asymptomatic joints may allow definite diagnosis during intercritical periods. (#5)
Analysis of Synovial Fluid

• View synovial fluid (SF) under a polarized light microscope*
  • All monosodium urate crystals (MSU) birefringent
  • 1/5 calcium pyrophosphate dihydrate (CPPD) crystals birefringent
• Always culture SF
  • Infected joints will still contain MSU and CPPD crystals*
• Search for MSU and CPPD crystals in all undiagnosed joint effusions*

Advanced Gout: Clinically Apparent Tophi

1. Photos courtesy of Brian Mandell, MD, PhD, Cleveland Clinic.
2. Photo courtesy of N. Lawrence Edwards, MD, University of Florida.
Advanced Gout: Radiographic Changes

- The characteristic gouty erosion is both destructive and hypertrophic, leading to “overhanging edges.”
- The joint space is often preserved until very late in the disease process.

Photo courtesy ACR Clinical Slide Collection on the Rheumatic Diseases, 1998.
Management Recommendations
Gout Treatment Goals

- Terminate the acute attack as rapidly as possible
  - Colchicine, NSAIDs, or Corticosteroids (Oral, Intra-articular)

- Protect against further attacks
  - Reduce the chance of crystal-induced inflammation
  - Decrease the chances of joint destruction and other long-term complications

- Treat hyperuricemia and prevent disease progression
  - Long-term correction of the metabolic problem
  - Lower serum uric acid sufficiently to deplete the total body urate pool. Target: Serum uric acid < 6.0 mg/dl.
Approach to Gout Management

Controlling Pain and Inflammation

- Acute Flare Pain
- Antiinflammatory Prophylaxis

Reducing Urate Burden

- NSAIDs
- Colchicine
- Glucocorticoids
- IL-1 inhibitors

Optimal Pharmacologic Gout Management

Edwards NL, Crystal-Induced Joint Disease in ACPMedicine Textbook, 2012
Management Recommendation: Importance of Patient Education

Patient education pertaining to beneficial lifestyle changes, compliance with long-term therapy, and the prevention of flares early in the course of ULT are core aspects of gout management. (#2)
Management Recommendation:
Address Modifiable Risk Factors and Comorbidities

Associated modifiable comorbidities and risk factors such as hyperlipidemia, hypertension, hyperglycemia, obesity, and smoking should be addressed as an important part of the management of patients with gout. (#3)
Management Recommendation: Colchicine, NSAIDs, and Corticosteroids Useful for Acute Attacks

- In patients with acute gout; oral colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids may be used as first-line treatments.

- The choice will depend on patient and physician preference, with consideration of comorbidities (especially a history of CKD and gastrointestinal disease).

- It may be necessary to continue treatment for an additional 7 to 10 days.(#4)
Other Options for Acute Gouty Inflammation

- Other choices
  - IA, IM or IV glucocorticoids
  - Off Label: ACTH gel s.c.
  - Off Label: IL-1 inhibitors
  - Topical ice

Terkeltaub R. AR&T, 2009
Management Recommendation:
Low Dose Colchicine is Effective and Best Tolerated

- For acute gout, low-dose colchicine (ie, 1.2 mg administered as soon as possible, followed by 0.6 mg 1 hour later) is effective and well tolerated.

- Colchicine should be continued (QD-BID as tolerated) for an additional 7 to 10 days or until the flare is resolved.

- High-dose colchicine is not indicated and should not be prescribed. (#5)
AGREE: Trial in Acute Gout

- Pivotal phase-3 trial examining the efficacy and safety of colchicine
- One of 17 clinical studies submitted to the FDA by URL Pharma
- Primary end point: 50% pain reduction at 24 hours without the use of rescue medication

Patients with acute gout (N=184)

High-dose colchicine\(^1\) (n=52)
(4.8 mg: 1.2 mg, then 0.6 mg/h × 6)

Low-dose colchicine\(^1\) (n=74)
(1.8 mg: 1.2 mg, then 0.6 mg in 1 h)

Placebo (n=58)

A responder is defined as a patient who achieved a ≥ 50% reduction in pain score and did not take rescue medication prior to the 24-hour post dose assessment.

* $P=0.034$ versus placebo.
† $P=0.034$ versus placebo.
AGREE: Adverse Events

*\( P \leq 0.05 \) vs low-dose and placebo.

NSAIDs

- Equivalent efficacy in gout amongst all NSAIDs

- Relatively contra-indicated in many common comorbid conditions
  - Peptic ulcer disease
  - Cardiovascular disease and hypertension
  - GI bleeds
  - Aspirin- or NSAID-induced asthma
  - Renal dysfunction
  - Postoperative patients
  - Warfarin

- Consider using PPI for gastric protection
Corticosteroids

• Effective as oral, intramuscular, or intra-articular agents

• Worsening of glycemic control in diabetics

• Infection risk

• Steroid “rebound” acute attack may recur if treatment not followed by NSAID or colchicine

• All side effects likely minimized by intra-articular administration
Management Recommendation: Intra-articular Steroids May Be Effective

For an acute attack, after sufficient precautions have been taken, intra-articular aspiration and injection of a long-acting steroid is an effective and generally well-tolerated treatment. (#6)

Rebound may occur and supplemental anti-inflammatory therapy is often needed.
Management Recommendation:
Indications for ULT

Urate-lowering therapy is indicated in patients with any of the following: recurrent attacks (> 1 attack per year), chronic arthropathy, tophaceous deposits, nephrolithiasis, or radiographic changes of gout.

Once initiated, ULT is considered a lifelong treatment recommendation. (#7)
The therapeutic goal of ULT is to prevent acute flares, prevent the development of tophi, help dissolve tophi, and prevent the development of chronic gouty arthropathy.

This is achieved by maintaining an SUA level of $< 6.0$ mg/dL, well below the saturation point for MSU of 6.8 mg/dL. (#8)
Urate Lowering Treatments

- **Urostatic agents: Xanthine oxidase inhibitors**
  - Allopurinol
  - Febuxostat (Uloric™)

- **Enzymatic-uricase**
  - Pegloticase

- **Uricosuric Agents: Contraindicated in over-producers**
  - Probenecid
  - Sulfinpyrazone

- **Medications that incidentally lower SUA**
  - Losartan
  - Fenofibrate
# Urate Lowering Therapy

## Important Considerations

- **Prophylaxis against gout flares**
  - Increased risk of flares with urate lowering therapy
  - Colchicine or NSAIDs; sometimes glucocorticoids

- **Treating to target**
  - Serum urate to <6 mg/dl
    - May be <4 mg/dl in patients with tophi
  - DON’T TREAT ASSYMPTOMATIC HYPERURICEMIA

- **Duration of therapy – indefinite**
  - Lifelong risks of ULT

- **Adherence is often sub-optimal**

- **Uncertainty in chronic kidney disease**

- **Patient education**
Management Recommendation: Colchicine Is First Choice for Prophylaxis

- Prophylaxis against acute attacks during the first 6 to 12 months of ULT can be achieved by colchicine (given as tolerated, 0.6 mg once or twice daily) or an NSAID (with gastroprotection if indicated).

- Prophylaxis should be initiated 2 weeks prior to the implementation of ULT.

- The choice for prophylaxis should include an analysis of the comorbidities of the patient as well as the risks and benefits of the agent, which are shown below.

- Nonsteroidal anti-inflammatory drugs are currently not FDA approved for prophylaxis. (#13)

The expert panel recommends that colchicine be considered as the first choice for prophylaxis. Nonsteroidal anti-inflammatory drugs and corticosteroids are alternatives if colchicine is not tolerated or is not effective. Colchicine is the only FDA approved medication for prophylaxis.
Probenecid, a uricosuric agent, can be used as an alternative to a xanthine oxidase inhibitor in patients with normal renal function, but is relatively contraindicated in patients with nephrolithiasis and ineffective in the presence of renal insufficiency.

- Probenecid can be used together with allopurinol or febuxostat, if necessary, to achieve the target goal of lowering SUA to < 6.0 mg/dL.

- Dosing may begin at 500 mg daily, with titration monthly up to a maximum of 3 g per day in divided doses. (#12)
Management Recommendation: Xanthine Oxidase Inhibitors

- The xanthine oxidase inhibitors (allopurinol and febuxostat) are the agents of choice for ULT to reach the therapeutic target SUA level of < 6.0 mg/dL.

- The dose should be titrated to optimize safety and minimize the chance of precipitating an acute flare.

- Serum uric acid should be monitored to ascertain the achievement and maintenance of this goal.

- Appropriate laboratory monitoring for toxicity is indicated. (#9)
The Target Level of SUA

- Saturation of uric acid occurs at >6.8 mg/dL.

- Achieving SUA of <6 mg/dL results in:
  - ↓ MSU crystals in joints
  - ↓ frequency of flares/attacks
  - ↓ tophus size

- Lower target SUA levels are appropriate in patients with severe, tophaceous disease.

- Median dose to goal for allopurinol is ~380 mg/day.
Management Recommendation: Allopurinol

- Allopurinol should be started at a low dose (100 mg daily) and increased by 100 mg every 2 to 4 weeks (to a maximum allowable dose of 800 mg/day) as necessary to achieve the target SUA goal of < 6.0 mg/dL.

- If allopurinol toxicity occurs, it should be stopped immediately.

- Other treatment options include febuxostat or probenecid. (#10)
Management Recommendation: Febuxostat

- Febuxostat should be started at 40 mg daily and may be increased to 80 mg after at least 2 weeks of treatment, if necessary to achieve the target SUA goal of < 6.0 mg/dL.
- If toxicity occurs, febuxostat should be stopped immediately.
- Other treatment options include allopurinol or probenecid.
- However, allopurinol and febuxostat should not be coadministered. (#11)
CONFIRMS Efficacy in Renally Impaired Subjects

Proportion of Subjects With Mild-to-Moderate Renal Impairment With sUA <6 mg/dL at Final Visit

| Group               | % of Subjects | p-value  
|---------------------|---------------|-----------
| Febuxostat 40 mg    | 50%           | * p<.05   
| (n=479)             |               |           
| Febuxostat 80 mg    | 72%           | ** p<.05  
| (n=503)             |               |           
| Allopurinol 300/200 mg | 42%      |           
| (n=501)             |               |           

*p<.05 vs allopurinol.
**p<.05 vs ULORIC 40 mg.

Renal impairment was defined as baseline estimated CL\text{cr} < 90 mL/min.
Enzymatic Uricolytic Drugs

• Uricase (urate oxidase) catalyzes uric acid to allantoin
  • Allantoin is more soluble than uric acid
  • Humans and other higher primates lack this enzyme

• Fast-acting, potent decrease in serum urate and in tophi

• Native and recombinant bacterial uricases are available outside the U.S. for intravenous use
  • To treat tumor lysis syndrome
  • Not indicated for treatment of gout.

• Significant incidence of allergic reactions: all uricase of non-human origin
Effect of Urate-Lowering Therapy on the Velocity of Size Reduction of Tophi in Chronic Gout

Uricase (uric acid oxidase) catalyzes the conversion of uric acid to allantoin: A more soluble, readily excretable form.
Approach to Gout Management

Controlling Pain and Inflammation

Acute Flare Pain
- NSAIDs
- Colchicine
- Glucocorticoids
- IL-1 inhibitors

Antiinflammatory Prophylaxis
- Colchicine
- NSAIDs
- IL-1 inhibitors

Reducing Uurate Burden
- Allopurinol
- Febuxostat
- Probenecid
- Pegloticase
- Lesinurad
- BCX4208
- Arhalofenate

Optimal Pharmacologic Gout Management

* Not FDA approved

Edwards NL, Crystal-Induced Joint Disease in ACPMedicine Textbook, 2012
Management Recommendation: Pegloticase

- For patients who have refractory gout and/or resistant tophaceous disease, pegloticase is another treatment option. Pegloticase is administered by infusion and has a significant risk profile.

- Patients who may be candidates should be referred to health care professionals with expertise in the use of pegloticase.
Ideal Candidate for Pegloticase

- Tophaceous disease, or
- Chronic synovitis, or
- Repetitive and frequent attacks of gout, or
- Unresponsive to standard ULT with one or more of the above issues
- De-bulking agent
Pegloticase
Resolution of Tophi

Baseline

Week 15

Sundy and Hershfield, unpublished data
Uric Acid Response during Biweekly (q2wks) Treatment with Pegloticase or Placebo

Biweekly Treatment Group

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Baseline</th>
<th>Month 3</th>
<th>Month 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>q2wks pegloticase</td>
<td>85</td>
<td>71</td>
<td>59</td>
</tr>
<tr>
<td>Placebo</td>
<td>43</td>
<td>43</td>
<td>39</td>
</tr>
</tbody>
</table>
Secondary Endpoints

- Tophus resolution
- Reduction in gout flares
- Reduction in tender and swollen joint counts
- Improvement in quality of life (SF-36)
- Improvement in functional status (HAQ-DI)
Tophus Resolution

26 March 2007

26 September 2007
Reduction in Gout Flares

Continued Improvement in Flare Burden with Pegloticase Over 18 Months

*P<0.05, pegloticase vs placebo

- Q2W
- Q4W
- Placebo

Months 1-3 and Months 4-6: data from double-blind studies (ITT)
Months 7-9 through Months 16-18: OLE treatment
Radiographic Outcomes

- No data was collected in the phase 3 program
- Radiographic scoring system recently proposed for gout*
- Virtually no data on radiographic outcomes in gout

*Dalbeth, et. al., Arthritis Care and Research, Vol 57, No. 6. August 2007
Radiographic Outcomes
Radiographic Outcomes
考虑将患有痛风的患者转诊至风湿病学家或肾脏病学家的建议包括：

- 确认诊断，特别是在有非典型表现的患者中
- 管理难治性病例时
  - 当SUA水平<6.0 mg/dL不能达到时
  - 即使看似已得到充分治疗，仍反复发作
  - 患者出现持续的和/或广泛的慢性痛风
  - 危重患者的管理
  - 考虑复杂治疗方案（#16）
Treatment Pearls

• Treat associated co-morbidities and address risk reduction behavior

• Initiate urate lowering therapy (ULT) in patients with two or more attacks a year

• Do not start ULT during an acute attack

• Do not discontinue ULT if patient on ULT has an acute attack

• Allopurinol is drug of choice for initial ULT

• Uricosurics useful in allopurinol allergic patients with normal renal function, under-excretion, and no history of nephrolithiasis

• Uricosurics – not indicated in overproducers

• Use concomitant prophylaxis when initiating ULT to prevent treatment induced attacks

• Measure serum uric acid levels every 3-6 months. Adjust medications until a target uric acid of <6 mg/dl is obtained

• Data continue to support the decision to diagnose gout using clinical characteristics rather than mandating crystal identification.

• Although studies have shown that SUA levels of > 6.0 mg/dL are a significant risk factor for gout,\textsuperscript{82-85} they are always a reliable diagnostic tool because approximately 14% of patients with acute gout presented with SUA levels of < 6.0 mg/dL.\textsuperscript{109} Conversely, some people with high SUA may never develop gout. Serum uric acid should be used in combination with clinical criteria and response to gout treatment to arrive at a diagnostic decision.

• Research has focused on the interaction of gout with typically associated risk factors and comorbid conditions. Strong associations have been demonstrated between gout and metabolic syndrome,\textsuperscript{110-112} CVD,\textsuperscript{32, 33, 50, 113} and CKD.\textsuperscript{33}

• Reference numbers are those from PostGraduate Medicine Reference
• The use of nonpharmacologic measures in the treatment of patients with gout, particularly dietary aspects, has become more sophisticated.\textsuperscript{114}

• Gout therapy relies on good patient education. Patients need to understand that gout treatment requires a lifelong commitment. Patients also need to know that the initiation of ULT results in acute gout attacks (mobilization flares) and that these attacks are a sign of effective therapy. Finally, they need to understand the importance of adhering to prophylaxis regimens.

• For effective management of an acute gout attack, treatment should begin within hours of first symptoms. Low-dose colchicine (1.2 mg as soon as possible, followed by 1 dose of 0.6 mg 1 hour later, for a total dose of 1.8 mg) is as effective and better tolerated than high-dose colchicine (1.2 mg followed by 0.6 mg every hour for 6 hours, resulting in a total dose of 4.8 mg).\textsuperscript{68}
• The benefits of reaching a target SUA level of < 6.0 mg/dL have been confirmed. For most patients, a target SUA between 5.0 and 6.0 mg/dL is safe and effective. Patients with incapacitating, severe, tophaceous gout may require SUA levels of < 4.0 mg/dL to see improvement. 87, 115, 116

• Allopurinol has been found to be safe and more effective at higher doses. It should be started at a low dose of 100 mg per day but can (with appropriate monitoring) be titrated up to 800 mg per day as necessary for a patient to achieve the target SUA level of 6.0 mg/dL. 92-94 It has been recommended that patients with renal impairment receive lower doses but recent studies report that this might not be required clinical practice.
• For patients who have not responded to or were not eligible to receive allopurinol, febuxostat (also a xanthine oxidase inhibitor with a slightly different mechanism of action) can be prescribed at unchanged doses for patients with mild-to-moderate renal or hepatic impairment. Intravenous pegloticase is indicated for patients with refractory and/or resistant tophaceous gout.

• Timely referral from primary care to rheumatology or nephrology may be the best option for patients with an uncertain diagnosis or in cases of severe disease.