2011 ACR Gout Guidelines Task Force

Preliminary Recommendations:

MANAGEMENT OF GOUT:
- URATE-LOWERING THERAPY (ULT)
- CHRONIC TOPHACEOUS GOUTY ARTHROPATHY

Robert Terkeltaub, MD
VAMC/University of California San Diego

GOUT CASE SCENARIOS:
To replicate mild, moderate, severe in-office presentations of gout
(#’s 1-6: intermittent symptoms without and with tophi; #’s 7-9: chronic tophaceous gouty arthropathy)

NOT A DISEASE CLASSIFICATION SCHEME

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Tophus or Tophi detected on Physical Exam</th>
<th>Frequency</th>
<th>CASE SCENARIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent</td>
<td>NO</td>
<td>Infrequent Symptoms (( \leq 1 ) attack/yr)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>Frequent Symptoms  (2-6 attacks/yr)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>NO</td>
<td>Very Frequent Symptoms (&gt; 7 attacks/yr)</td>
<td>3</td>
</tr>
<tr>
<td>Intermittent</td>
<td>YES</td>
<td>Infrequent Symptoms (( \leq 1 ) attack/yr)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td>Frequent Symptoms  (2-6 attacks/yr)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>YES</td>
<td>Very Frequent Symptoms (&gt; 7 attacks/yr)</td>
<td>6</td>
</tr>
</tbody>
</table>

DISCLOSURES:
Robert Terkeltaub MD

- GRANT SUPPORT: VA, NIH
- CONSULTANT: Takeda, Savient, ARDEA, BioCryst, URL, Regeneron, Novartis, Pfizer, Metabolex, Nuon, Chugai, Ajanta, Prescription Solutions
- SPEAKER: None

Chronic Tophaceous Gouty Arthropathy: CASE SCENARIOS

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Characteristics</th>
<th>CASE SCENARIO</th>
</tr>
</thead>
</table>
| Mild             | • Stable disease
                  | • Simple chronic tophaceous gouty arthropathy
                  | • Affecting 1 joint | 7
| Moderate         | • Stable disease
                  | • Simple chronic tophaceous gouty arthropathy
                  | • Affecting 2-4 joints | 8
| Severe           | • Chronic tophaceous gouty arthropathy of >4 joints
                  | OR
                  | • ≥1 unstable, complicated, severe articular tophus or tophi | 9
CASE SCENARIOS:
MILD Chronic Tophaceous Gouty Arthropathy
Stable, simple tophus limited to one joint (Scenario #7)

- Lack of drainage
- Lack of aggressive connective tissue mass or destructive effects
- Lack of high risk of infection
- Stable in size, or slow growth
- Lack of severe chronic, tophaceous joint inflammation

MODERATE Chronic Tophaceous Gouty Arthropathy
Stable, simple tophus affecting 2-4 joints (Scenario #8)

CASE SCENARIOS:
SEVERE Chronic Tophaceous Gouty Arthropathy:
Numerous, Complicated, or Unstable Tophi (Scenario #9)

- Tophi affecting more than 4 joints
  — OR —
- One or more Tophi demonstrating
  ✓ Drainage
  ✓ Aggressive mass or connective tissue destructive effects
  ✓ High risk of infection
  ✓ Very rapid growth
  ✓ Severe, chronic tophaceous joint inflammation

Outline of preliminary gout management recommendations:

- Diagnostic, Imaging, Co-Morbidity Considerations
- General Management Principles for all Patients

➢ ULT Domain
- Principles of Non-pharmacologic and Pharmacologic ULT
- Approach to Refractory Disease

➢ Chronic Tophaceous Gouty Arthropathy Domain

Summary of Gout Management Options and Objectives in Varying Disease Severity Case Scenarios 1-9

Measure

<table>
<thead>
<tr>
<th>No tophi on exam</th>
<th>Tophi detected on exam</th>
<th>Intermittent Symptoms</th>
<th>CTGA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet, alcohol, weight management, and co-morbidity and medication review</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Target serum urate should be lowered sufficiently to improve signs and symptoms of gout</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

PHARMACOLOGIC ULT

First line: SINGLE AGENT XOI titrated to maximum appropriate dose (Alternative: Probenecid)

- serum urate target not achieved

Combination: ORAL XOI + URICOSURIC ULT at maximum appropriate doses

- serum urate target not achieved

PEGLOTICASE

1 Finding of a tophus or tophi on imaging study, or CKD Stage 2-5, or ESRD, are appropriate indications for first line pharmacologic ULT in Scenario 1.

2 Failure of combination XOI and uricosuric therapy at maximum appropriate doses is an acceptable indication for consideration of Pegloticase therapy in Scenario 5.
Summary Preliminary Recommendations in Diagnosis of Gout that Impact on Therapy

• The diagnosis of gout should be definitive before initiation of ULT in all case scenarios

• Recommended measures for diagnosis of gout extend beyond clinical classification criteria, synovial fluid aspiration/crystal analysis

• Particular focus of the panel:
  – High Resolution Ultrasound

Preliminary Recommendations on Imaging Measures in Supporting Diagnosis of Gout and with the Potential to Impact on Therapy

– High resolution ultrasound finding of “Double Contour Sign” is a valid and useful measure to detect urate crystal deposition
– High resolution ultrasound findings suggestive of tophus or tophi
– Plain radiography findings such as erosion
– Advanced imaging (eg, CT, dual energy CT [DECT]):

High resolution ultrasound finding of “Double Contour Sign” by itself NOT an appropriate indication for pharmacologic ULT

High Resolution Ultrasound: Preliminary Recommendation as Imaging Approach in Gout

“DOUBLE CONTOUR SIGN”:
Accepted by TFP as evidence for urate crystal deposition

Image of a big toe with a double contour sign attached (dorsal long axis view)

Image provided by Dr. Ralf Thiele, University of Rochester

Preliminary General Recommendations for MANAGEMENT OF ALL PATIENTS with Gout

➢ Primary Principle: Communicate and educate patients on treatment objectives and adherence

• Assess gout symptom severity and tophus burden
• Consider cause(s) of hyperuricemia
• Diagnose and treat co-morbidities
• Communicate and initiate diet, lifestyle recommendations
• Eliminate non-essential prescription of specific serum urate-elevating medications
  – Thiazide and loop diuretics
  – Niacin
  – Calcineurin inhibitors
Specific Recommendations:
CO-MORBIDITY CHECKLIST for Gout patients
Appropriate to consider, and, if indicated, evaluate:  

- Serum urate-elevating medications
- Hypertension
- Metabolic syndrome, Type 2 Diabetes Mellitus
- CKD, renal disease
- Excessive Alcohol Use
- Obesity, Dietary Factors
- Hyperlipidemia, Modifiable risk factors for CAD or stroke
- History of urolithiasis
- In selected cases, potential genetic and acquired causes of uric acid overproduction
- Lead toxicity

**Preliminary: Indications for Pharmacologic ULT**

Any patient with established diagnosis of gouty arthritis and
- Tophus or tophi by clinical exam or imaging study
- Frequent attacks of gouty arthritis (≥ 2 per year)
- CKD Stage 2-5, ESRD
- Uric acid urolithiasis

Start pharmacologic ULT + Start Pharmacologic Gout Attack Prophylaxis

<table>
<thead>
<tr>
<th>Avoid</th>
<th>Limit</th>
<th>Encourage</th>
</tr>
</thead>
</table>
| • Organ meats high in purine content | • Serving Sizes of:  
  - Beef, Lamb, Pork  
  - Lean meat  
  - Seafood with high purine content (eg sardines)  
  - Shellfish | • Low fat or non fat dairy products  
  • Vegetables |
| • High fructose corn syrup-sweetened drinks or foods | • Naturally sweet fruit juices  
  • Table sugar, and sweetened beverages and desserts  
  • Table salt, including in sauces and gravies | |
| • Alcohol including beer  
  • Concentrated binges of caffeinated beverages including coffee | |

*Lack of consensus: Ascorbate, cherries, nuts, legumes

**Preliminary Specific Recommendations:**
GENERAL HEALTH, DIET, LIFESTYLE MEASURES IN GOUT PATIENTS:
for all grades

- Achieve optimal BMI
- Healthy overall diet
- Exercise
- Smoking cessation
- Stay well hydrated

**Preliminary: Indications for Pharmacologic ULT**

- Xanthine Oxidase Inhibitor
- Allopurinol OR Febuxostat
- Uricosuric agent
- Probenecid

Initiate 1st line ULT AND Treat to SUA target

Monitor for
- Side Effects
- SUA (q6-12 mo)

Evaluate ongoing gout symptoms and signs

Yes

SUA target achieved?

Ongoing symptoms

No symptoms

No

Yes

 Maintain serum urate <6.0 mg/dL indefinitely (by non-pharmacologic measures, and any necessary pharmacologic ULT)

Ultimately Discontinue Prophylaxis

Initiate Pharmacologic Anti-inflammatory Prophylaxis

Refactory Gouty Arthritis

Continue Gout Attack Prophylaxis

Refactory Hyperuricemia
Summary Preliminary Recommendations for MANAGEMENT OF HYPERURICEMIA in Gout

- Xanthine Oxidase Inhibition (XOI) endorsed as primary first line pharmacologic ULT
- Probenecid endorsed as alternative first line therapy

- Pharmacologic ULT can be started during an acute gout attack, providing that effective anti-inflammatory management has been achieved
  (to be defined in talk by D Khanna)
- Monitor serum urate regularly

Preliminary Recommendations for SUA TARGET WITH ULT in Gout

- Goal of ULT is SUA target, at a minimum, of < 6mg/dL in all case scenarios
- Target Serum Urate should be lowered sufficiently to improve signs and symptoms of gout, which may involve lowering to below 5 mg/dL

Velocity of Tophus Reduction Accelerates as Serum Urate drops Below 5 mg/dL

Summary Preliminary Recommendations for ALLOPURINOL IN ULT for Gout

- Prior to initiation, consider HLA-B*5801 in selected high risk patients for severe hypersensitivity
  (eg, Han Chinese; Asians with CKD stage 3-5)
- Starting dose <100 mg/d, and lower than 100 mg/d in stage 4 or worse CKD
- Gradually titrate maintenance dose upwards every 2-5 weeks to appropriate maximum dose, in order to treat to chosen SUA target
- Dose can be raised >300 mg/d with monitoring for drug toxicity
  (eg, pruritis, rash, elevated hepatic transaminases)

Meta-Analysis:
HLA-B*5801 Linkage to Severe Allopurinol Hypersensitivity Reactions (AHS/DRESS, SJS, TEN)


• Matched-control studies:
  OR 96.60, 95%CI 24.49-381.00, p<0.001
• Population-control studies:
  OR 79.28, 95%CI 41.51-151.35, p<0.001

Summary Preliminary Recommendations for URICOSURIC ULT in Gout

• History of urolithiasis contra-indicates primary uricosuric ULT
• Urinary uric acid should be measured before uricosuric ULT
• Elevated 24hr urine uric acid or high urine uric acid on spot urine collection contra-indicates uricosuric ULT
• Continue to monitor urinary uric acid during uricosuric ULT
• Consider urine alkalization (eg, K+ CITRATE), with monitoring of urine pH

LACK OF CONSENSUS: UNDISSOCIATED URINE URIC ACID ASSAY

Specific Preliminary Recommendations for CHOICE OF URICOSURIC ULT in Gout

➢ PROBENECID FIRST CHOICE AMONG URICOSURICS
➢ USE PROBENECID ONLY AFTER FAILURE OF ≥1 OTHER ULT

• If CrCl <50, other ULTs favored over probenecid
• Consider other agents with uricosuric effects (eg, FENOFIBRATE, LOSARTAN, ASCORBATE) where appropriate
• Addition of uricosuric to XOI drug is an effective therapeutic approach

Initiate 1st line ULT AND Treat to SUA target

Initiate Pharmacologic Anti-inflammatory Prophylaxis

Monitor for
• Side Effects
• SUA (q6-12 mo)

Yes

SUA target achieved?

No

Refractory Hyperuricemia
Summary Preliminary Recommendations for REFRACTORY or DIFFICULT TO TREAT Gout patients

• Attempt upwards dose titration of a Xanthine Oxidase inhibitor (XOI) when serum urate target has not been met

• If upward titration of initial ULT agent does not meet target
  – Consider ADDING URICOSURIC (if on XOI)
  – Consider CHANGING XOI
  – Consider ADDING XOI (if on Uricosuric)

Preliminary: Additional gout management options and objectives in CHRONIC KIDNEY DISEASE (CKD) and END STAGE RENAL DISEASE (ESRD)

• CKD STAGE 2-5 OR ESRD patient with gout:
  – Sufficient indication for first line pharmacologic ULT in any gout patient

• For specific scenario of a DIALYSIS patient with gout:
  – Serum urate should not be measured during dialysis session
  – Hemodialysis is often associated with reduction of symptomatic arthritis in those with pre-existing gout
  – For dialysis patients with hyperphosphatemia, sevelamer should be considered in ULT

Pegloticase: Preliminary Summary Recommendations for REFRACTORY or DIFFICULT TO TREAT Gout patients

• Pegloticase appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, conventional and appropriately dosed ULT

• LACK OF CONSENSUS:
  Appropriate duration of pegloticase therapy relative to intended and achieved decrease in symptoms and signs of gout, including decrease in tophus size

• Pegloticase therapy not recommended as first line ULT agent for any case scenarios

HIGHLIGHTS OF PRELIMINARY SYSTEMATIC GOUT/HYPERURICEMIA MANAGEMENT RECOMMENDATIONS:

• Ultrasound: Useful Imaging Modality in Symptomatic Gout
• Specific Co-Morbidity and Diet Advice Checklists Established
• Pharmacologic ULT Algorithm Developed
• Consensus: “SUA Target to Improve Gout Symptoms and Signs”
• Allopurinol: Starting Dose, Selective Pharmacogenomics
• Combination Oral ULT Endorsed for Broad Case Scenarios
• Pegloticase Recommendations in Distinct Case Scenarios
• Specific Recommendations for Management of Refractory Disease Developed in:
  – Chronic Tophaceous Gouty Arthropathy
  – Gout CKD Stage 3 or Worse
Limitations in Assessing Evidence for these Gout Domains

- Add-on vs. Substitution vs. “All Comers” 1 Agent Rx
- “Real World” Patients (eg, selection due to prior failure of allopurinol therapy) vs. Industry-Sponsored Clinical Trials
- Non-titrated Allopurinol vs. Titrated Febuxostat
- Placebo Comparator, Low Numbers/Duration: Pegloticase
- Cross-Sectional, Prospective, or Retrospective Designs
- Epidemiology, and Internet-Based Case Crossover Studies vs. Prospective, Controlled Clinical Trials: eg, Diet, Alcohol, SUA, Disease Activity

Issues and Limitations in Assessing Outcomes Evidence in these Domains in Gout

- Outcomes, Clinical Activity, Response Criteria Uneven, Poorly Defined, or Surrogate: eg, Clinical Activity (Gout Attack Frequency, Severity, Duration) Serum Urate (eg, <6, <5), Joint Damage, QOL
- QOL Instruments: Variable, Evolving
- Index Tophus: Visible Resolution or Size Reduction Velocity: Criteria, Differing Tophus Sites, ? Role of Imaging
- Imaging: Not Yet Utilized in Outcomes Analyses

Serum Urate Reduction Using Allopurinol Dose Escalation Above Previous Renal Dose Adjustment in Gout, Including Those With Renal Impairment

Extra slides

Evidence Reviewed: High Risk Populations re HLA-B*5801 Linkage to Severe Allopurinol Hypersensitivity Reactions (AHS/DRESS, SJS, TEN)

Examples:

<table>
<thead>
<tr>
<th>HLA-B*5801 Prevalence</th>
<th>Odds Ratio of Severe Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han Chinese: 9%</td>
<td>~580:1</td>
</tr>
<tr>
<td>Koreans: 12.2%</td>
<td>~380:1 with CKD stage 3-5</td>
</tr>
<tr>
<td>Thai: &gt;6%</td>
<td>&gt;100:1</td>
</tr>
</tbody>
</table>

Comparison to Caucasians:

Caucasians: 1-3% in most Up to ~80:1 (lower negative predictive value)

HLA-B*5801 screening endorsed for high risk groups:

- PCR screening (followed by sequencing for inconclusive results (in ~10% of PCR tests))

Specific Recommendations: URINE URIC ACID SCREENING FOR SELECTED GOUT PATIENTS

- Gout onset before age 25
- History of urolithiasis

Evidence for Urinary Uric Acid Monitoring Before and During Uricosuric Therapy

Velocity of Tophus Reduction Accelerates as Serum Urate drops Below 5 mg/dL

Table 1. Initial serum uric acid levels and outcome measures during followup

<table>
<thead>
<tr>
<th>Allopurinol</th>
<th>Benz bromaronate</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 24</td>
<td>n = 25</td>
<td>n = 14</td>
</tr>
<tr>
<td>Serum urate at baseline (mg/dl)</td>
<td>8.78 ± 1.34</td>
<td>9.24 ± 1.66</td>
</tr>
<tr>
<td>Mean serum urate during followup (mg/dl)</td>
<td>5.37 ± 0.79*</td>
<td>4.22 ± 1.01</td>
</tr>
<tr>
<td>Diameter of tophus (mm)</td>
<td>16.2 ± 6.1</td>
<td>16.0 ± 9.4</td>
</tr>
<tr>
<td>Time until tophus resolution (months)</td>
<td>29.1 ± 8.3*</td>
<td>13.5 ± 5.8</td>
</tr>
<tr>
<td>Velocity of reduction (mm/month)</td>
<td>0.57 ± 0.18*</td>
<td>1.21 ± 0.67</td>
</tr>
</tbody>
</table>

*Comparison between groups P < 0.01.

Initiate 1st line ULT therapy

- Xanthine Oxidase Inhibitor
  - Allopurinol
  - Febuxostat
- Uricosuric agent
  - Probenecid

Monitor for:
- Side Effects
- SUA (q6-12 mo)

Evaluate ongoing gout symptoms and signs

SUA target achieved?

Yes

No

Refractory Hyperuricemia

Refractory Gouty Arthritis

Continue Gout Attack Prophylaxis

Discontinue Prophylaxis after the greater of:
- At least 6 months of therapy
- 3 months after achieving target SUA (for gout with no tophi on clinical exam)
- 6 months after achieving target SUA (for gout with tophi or tophi seen on clinical exam)

Initiate Pharmacologic Anti-Inflammatory Prophylaxis

either
- Prior to ULT OR
- Concurrent with ULT

Maintain serum urate <6.0 mg/dL indefinitely (by non-pharmacologic measures, and any necessary pharmacologic ULT)