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Class Update: Drugs for Gout

Date of Review: January 2017 **Date of Last Review:** May 2015 (lesinurad, July 2016)

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
The Oregon Drug Use Review / Pharmacy and Therapeutics Committee requested specific clinical criteria to guide prescribers to appropriate step therapy for management of hyperuricemia and gout flares.

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Research Questions:

1. In adult patients with a history of gout, is there new evidence for differences in efficacy or effectiveness between drug therapies used for prevention and treatment of acute gout attack?
2. Does current evidence suggest appropriate pharmacological step therapy for the prevention of acute gout attacks in adult patients with recurrent gout attacks?
3. In adult patients with a history of gout, is there new evidence for differences in harms between drug therapies used for prevention and treatment of acute gout attacks?
4. Are there subpopulations based on co-morbid conditions (i.e., renal insufficiency, peptic ulcer disease) or gout history (i.e., acute versus chronic) in which one drug may be more effective or associated with less harm than other drugs used for prevention of gout flares?

Conclusions:

- Drugs for gout were reviewed in May of 2015, as well as a new drug review in July of this year. Since the last class update there has been one high quality systematic review on the management of gout from the Agency for Healthcare Research and Quality (AHRQ), one systematic review on the use of allopurinol with urate lowering therapy (ULT) and 2 new evidence-based guidelines, one from the European League Against Rheumatism (EULAR) and one from the American College of Physicians (ACP).[1, 2, 3, 4]
- Evidence on drug therapies was insufficient for outcomes of joint tenderness, swelling, activities of daily living and patient global assessment.
- Efficacy outcomes studied were the following: pain, serum urate levels, and incidence of gout attacks.
    - There is high strength of evidence to support the use of NSAIDs, colchicine and systemic corticosteroids for pain relief in patients with acute gout.[1,3,4]
    - Serum urate levels were found to be reduced with allopurinol and febuxostat based on high strength of evidence.[1]
    - Moderate evidence found low dose colchicine to offer similar pain relief with less adverse events as high-dose colchicine,[1] therefore, low-dose is recommended when using colchicine for the treatment of acute gout.[4]

- Use of prophylactic therapy with low-dose colchicine or low dose NSAIDs reduces the risk of an acute gout attack in patients starting on ULT based on high strength evidence.[1]
- There is high quality evidence for the use of allopurinol first line for those patients who are candidates for ULT therapy.[3]
- There is high quality evidence that low dose colchicine or low dose NSAIDs at the start of ULT initiation, reduces the risk of an acute gout attack by a similar amount.[1,4] EULAR guidelines recommend flare prophylaxis for the first 6 months with colchicine, with NSAIDs as an alternative option.[3]
- Combinations of allopurinol and uricosurics are recommended for patients requiring additional therapy to obtain target serum urate levels.[3]
- There was low level evidence that targeting a specific urate level reduces the risk of gout attacks.[1]
- There is moderate evidence that long-term ULT should not be initiated in the majority of patients after the initial attack or in patients with infrequent attacks.[4]
- Evidence is insufficient to make conclusions on efficacy or safety in specific subgroup populations.[1]

- In 11 trials evaluating the safety of allopurinol and ULT combination therapy, most adverse reactions were of mild to moderate severity.[2] Moderate evidence found elevated liver function tests were the most common adverse event leading to withdrawal in studies of allopurinol and febuxostat. There is moderate evidence that more probenecid-treated patients compared to allopurinol discontinued therapy (26% vs. 11%). Allopurinol was associated with a 7% incidence of withdrawal due to rash compared to 3% with probenecid; however, gastrointestinal (GI) adverse reactions were more common with probenecid compared to allopurinol (23% vs. 7%, respectively).[2]
- Harms associated with acute gout treatment were GI adverse reactions experienced with colchicine and NSAIDs and both need dose reductions in patients with renal impairment. Systemic corticosteroids and adrenocorticotropic hormone (ACTH) derivatives were associated with elevated blood glucose levels, dysphoria, immune suppression, and fluid retention with short-term use.[1] Adverse events were found to be similar between allopurinol (300 mg) and febuxostat 40 mg based on high level evidence. Most common adverse events were rash (sometimes serious) and abdominal pain with allopurinol and diarrhea and musculoskeletal pain with febuxostat (and rarely skin reactions).

Recommendations:

- Continue preferred drug list (PDL) status for allopurinol as the first-line ULT.
- Recommend clinical prior authorization (PA) criteria for non-preferred drugs (**Appendix 3**).
- After comparison of drug costs in executive session, no changes to the PDL were recommended.

Previous Conclusions:

- There is low quality evidence a greater proportion of patients respond to treatment, defined as a 50% or greater decrease in pain score, with high-dose (4.8 mg over six hours) colchicine compared to placebo (absolute risk difference 28%; RR 2.16; 95% CI 1.28 to 3.65; NNT 4) and low quality evidence significantly decreases inflammation scores more than placebo (absolute risk difference 45%; RR 10.50; 95% CI 1.48 to 74.38).
- There is low quality evidence of no significant difference between high- (4.8 mg over six hours) and low-dose (1.8 mg over one hour) colchicine in treatment response (RR 0.86; 95% CI 0.53 to 1.41) with fewer gastrointestinal events with low-dose colchicine.[1]
- There is insufficient evidence of any significant difference between allopurinol and febuxostat for treatment of acute gout flares.
- There is low-quality evidence of uncertainty around the difference in prevention of acute gout attacks between probenecid and allopurinol after 18 months of treatment (53% vs. 55%; RR 0.96; 95% CI 0.53 to 1.75) with no significant difference found.

- The U.S. Food and Drug Administration (FDA) approved lesinurad 200 mg daily as an adjunct with a xanthine oxidase inhibitor (allopurinol or febuxostat) for hyperuricemia based on 3 unpublished, multinational, phase 3 clinical trials of unclear risk of bias and uncertain applicability. Though the 400 mg daily dose was studied, the FDA denied approval of the dose based on increased risk for major cardiovascular and renal events compared to placebo.
    - There is insufficient comparative evidence that lesinurad is superior to existing anti-gout agents when used in combination with a xanthine oxidase inhibitor.
    - There is insufficient evidence that lesinurad in combination with a xanthine oxidase inhibitor demonstrates efficacy in reduction of gout flares, provides symptom relief, results in function improvement, or improves health-related quality of life versus a xanthine oxidase inhibitor alone.
    - There is insufficient evidence for use of lesinurad as monotherapy for management of hyperuricemia.
    - There is low quality evidence that daily doses of lesinurad 200 mg in combination with allopurinol may result in over half of patients achieving a serum uric acid less than 6 mg/dL over 6 months [54% vs. 28% with placebo, respectively; RR 0.26 (95% CI, 0.17 to 0.36; p<0.0001) and 55% vs. 23%, respectively; RR 0.32 (95% CI, 0.23 to 0.41; p<0.0001)]; similarly, in combination with febuxostat, there is low quality evidence adjunctive use of lesinurad 200 mg daily may result in over half of patient achieving a serum uric acid less than 5 mg/dL over 6 months [57% vs. 47% with placebo; RR 0.10 (95% CI, -0.03 to 0.23; p=0.1298)]. Lesinurad did show statistically significant reductions in serum uric acid levels relative to placebo over 6 months (range -0.79 to -1.08 mg/dL). The clinical significance of these reductions and how it relates to prevention of gouty attacks is unclear.
    - There is moderate quality evidence that lesinurad treatment is associated with an increased risk of renal adverse events, including reversible and non-reversible elevations in serum creatinine and acute renal failure.
    - There is insufficient evidence that any subgroups based on a particular demographic may benefit from lesinurad more than the general population for which it has been studied. All patients studied were adults, mostly obese white males between 21 to 82 years of age.

Previous Recommendations:

- Continue to include one xanthine oxidase inhibitor as preferred on the PDL for the treatment of chronic gout and hyperuricemia.
- Maintain Zurampic® (lesinurad) as non-preferred on the PMPDP.

Background:

Gout is the most common form of inflammatory arthritis.[5] The pathophysiology of gout stems from rising serum urate levels that exceed the saturation point in the blood leading to crystals that deposit in cartilage, bones, tendons and other sites. This increase in serum urate can be from overproduction or reduced excretion of uric acid resulting in inflammatory joint swelling and pain.[1] The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classifies gout based on presence of monosodium urate monohydrate (MSU) crystals in the symptomatic joint, bursa or tophi or at least 1 episode of swelling, pain or tenderness in a peripheral joint or bursa with additional clinical criteria also being met.[6] The ACP recommends synovial fluid analysis in patients with acute gout when diagnostic testing is indicated.[7]

Gout is characterized by acute attacks (lasting 7-14 days) that are self-limiting and are accompanied by symptoms of pain and inflammation that often presents in the toe but can occur in other joints. Chronic gout stems from acute attacks that increase in duration and become persistent.[1] Asymptomatic hyperuricemia can also occur; however, there is no evidence to support treatment as a preventative strategy for progression to symptomatic gout.[1] The risk of acute gout attacks can be predicted by serum urate levels. Guidelines recommend serum urate levels less of than 6 mg/dL for patients with gout and less than 5 mg/dL in patients with significant gout.[1,3,8] Tophi, which are uric acid crystals that deposit in the joints and other areas, may develop in patients with chronic gout and hyperuricemia. Important outcomes to consider when assessing treatment for gout are: serum and/or uric acid levels, gout attacks, development of tophi, and progression from acute to chronic gout.

Risk factors for the development of gout include obesity, excessive alcohol intake, dietary factors, medications that increase uric acid levels and chronic kidney disease.[4] Patients with a diagnosis of gout are advised to avoid organ meats, high fructose corn syrup-sweetened sodas and other foods, alcohol overuse, and alcohol abstinence during acute gout attacks.[8] Patients are also encouraged to minimize impact of comorbidities by optimizing weight, regular exercise, diet modifications, minimal alcohol consumption, and treatment of underlying cardiovascular (CV) risk factors.[9]

Selection of gout therapies is dependent on the diagnosis of acute or chronic gout (Table 1).[1,3,9] Treatment for acute gout should be initiated within 24 hours of the onset of the attack.[5] The ACR recommends treatment based on severity of pain and the number of joints involved.[5] Monotherapy with oral NSAIDS, systemic corticosteroids, or colchicine is recommended for mild to moderate severity of acute gout (visual analog score [VAS] of less than 6 and involvement in 1-3 small joints or 1-2 large joints). Combination therapy is indicated for polyarticular attacks with severe pain. Combination options in severe cases include: 1) NSAIDs and colchicine; 2) oral corticosteroids and colchicine; or 3) intra-articular steroids and one of the other oral treatment options.[1,5] In severe refractory cases of gout, use of a biologic interleukin-1 (IL-1) inhibitor can be considered. ACTH subcutaneous injections can be an option in patients who are not able to take medications by mouth.[5]

Management of chronic gout focuses on urate reduction through ULT (table 1).[1,3,9] Guidelines recommend ULT in patients with a gout diagnosis and the following: tophus or tophi, frequent attacks (≥ 2 attacks/year), chronic kidney disease stage 2 or worse or a history of past urolithiasis.[8] Serum urate levels should be checked every 2-5 weeks during the titration phase and every 6 months once a maintenance dose is determined. Xanthine oxidase inhibitors (XOI), allopurinol and febuxostat, are recommended as first-line pharmacological treatment options. Alternative pharmacological options are uricosurics (probenecid and lesinurad).[5] Guidelines prefer an XOI over uricosurics for chronic gout. Lesinurad is an alternative to probenecid due to limited evidence of efficacy and renal concerns, such as reversible and non-reversible elevations in serum creatinine and acute renal failure. Combination therapy with a XOI and probenecid are recommended if XOI monotherapy fails to lower serum urate levels to target.[8] If patients develop an acute gout attack on ULT, recommendations are to continue ULT while treating the acute attack.

Combination therapy with ULT and acute gout medications are recommended for patients experiencing symptoms of an acute attack and are candidates for chronic treatment. Historically, it is recommended that ULT be started 2 weeks after an acute flare subsides, as ULT may increase acute gout attacks initially; however, there is limited evidence that this delay is not required.[8] Low dose colchicine is recommended first-line for prophylaxis and low dose NSAIDs as a first-line alternative. Low dose prednisone or prednisolone are also used as an alternative to first-line agents in some patients.[5] Prophylaxis is recommended for at least 6 months. Dietary factors (alcohol use, meat intake, shellfish intake, intake of high fructose foods) have shown to play a role in the risk for gout and can be recommended as adjunctive measures to pharmacotherapy.

Table 1. Treatments used for the Management of Gout[1,8,5,10]

Drug	Mechanism of Action
Acute Gout Management	
NSAIDs†	Anti-inflammatory
Corticosteroids (intraarticular or oral†)	Anti-inflammatory
Colchicine†	Microtubule disrupting agent
Pituitary adrenocorticotropic hormone (ACTH)	Anti-inflammatory

Urate-lowering therapy (ULT)	
Allopurinol	Xanthine oxidase inhibitor
Febuxostat	Xanthine oxidase inhibitor
Probenecid	Uricosuric - prevention of renal reabsorption of uric acid and increase excretion
Lesinurad*	Uricosuric – increase excretion of uric acid
* To be used as an adjunct with a xanthine oxidase inhibitor † Also recommended for gout prophylaxis	

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

AHRQ – Management of Gout
In March of 2016, AHRQ completed a systematic review on the management of gout in adult patients with a focus on the primary care setting. Included studies were assessed for risk of bias using the Cochrane Risk of Bias Tool and a modified AMSTAR tool was used for the determination of the quality of systematic reviews.[1] Key questions focused on the treatment of acute gout, dietary and lifestyle management of gout, pharmacological management of hyperuricemia in gout patients, treatment and monitoring of patients with gout and discontinuation of treatment for patients on acute or chronic gout medications. Results of the literature search yielded 143 articles for inclusion into the review.[1] The study population included in the analysis was deemed to have moderate applicability to patients seen in primary care. Eight percent of the included studies specifically stated that patients were from the primary care setting which have been shown to have at least 10% less incidence of tophi compared to trials including patients from other settings such as hospitals.

Acute Gout Treatment
For the treatment of acute gout, 15 studies were included, 10 were systematic reviews and 5 were randomized controlled trials. The randomized controlled trials were small with the number of participants ranging from 57-190. Study participants were adult patients with a diagnosis of acute gout. About 90% of participants were male with a mean age of 54 years (when reported). Findings related to specific drug therapies are presented in Table 1.[1] There was insufficient evidence for the outcomes of joint swelling, tenderness, activities of daily living, and patient global assessment. Assessment of efficacy based on patient demographics, comorbid conditions, disease severity, clinical presentation or lab values was insufficient. Colchicine and NSAIDs were associated with GI adverse

events and require dose reductions in patients with renal impairment. Systemic corticosteroids and ACTH derivatives were associated with elevated blood glucose levels, dysphoria, immune suppression, fluid retention.[1]

Table 2. Evidence for Drugs Used in Acute Treatment of Gout[1]

Drugs *(i.e., NSAIDs, corticosteroids, colchicine, ACTH, IL-1B receptor antagonists*)*	**Findings**	**Strength of evidence**
Colchicine	Pain relief	High
Low-dose colchicine (1.2 mg initially followed by 0.6 mg one hour later) vs. high-dose colchicine (1.2 mg initially followed by 0.6 mg each hour for the next 6 hours)	Pain relief similar with less adverse events in low-dose group	Moderate
NSAIDs	Pain relief	High
NSAIDs	Similar effectiveness between all NSAIDs used for gout	Moderate
Systemic corticosteroids	Pain relief	High
Animal-derived ACTH formulations *(i.e., corticotropin [H.P. Acthar® Gel])*	Pain relief	Moderate
** No new evidence was found for IL-1B receptor antagonists*		

Dietary and Lifestyle Management of Gout

Six new trials, 3 observational studies and 5 systematic reviews evaluated the role of diet in gout, including Traditional Chinese Medicine (herbs and acupuncture).[1] Randomized controlled trials ranged from 29-1042 participants, with the larger studies funded by Beijing University of Chinese Medicine. Evidence on the impact of dietary changes on improving gout symptoms was insufficient. Similarly, evidence for the reduction of serum urate levels as a result of dietary changes was insufficient. The role of Traditional Chinese Medicine provided insufficient evidence in treating the symptoms of gout.

Hyperuricemia Management in Patients with Gout

Forty-five studies provided evidence on efficacy and safety of pharmacological hyperuricemia management.[1] Evidence for ULT were based on studies with low to high risk of bias in adult patients with chronic gout. Findings for efficacy outcomes are the following:

- There is high strength of evidence of no difference in serum urate lowering between febuxostat 40 mg and allopurinol 300 mg.
- There is high strength of evidence that prophylaxis with low dose colchicine or low dose NSAIDs at the start of ULT initiation, reduces the risk of an acute gout attack by a similar amount.
- There was insufficient evidence to determine the effect of feboxostat compared to allopurinol 300 mg on the presence of tophi.
- Moderate strength of evidence supports longer treatment courses (>8 weeks) of colchicine or NSAIDs, with ULT, for gout attack prevention compared to shorter courses.

High strength evidence shows that the risk of acute gout attacks is not reduced with ULT within the first 6 months; however, attacks were decreased after approximately 1 year of ULT based on moderate evidence. The use of ULT does indeed decrease serum urate levels based on high strength evidence.[1] The evidence for the role of dietary changes on serum urate levels are insufficient. Adverse events most associated with ULT are rash for allopurinol (sometimes

serious) and abdominal pain, diarrhea and musculoskeletal pain (and rarely skin reactions) with febuxostat. Risk of adverse events were found to be similar between allopurinol (300 mg) and febuxostat 40 mg based on high strength evidence.

Monitoring Treatment for Gout

Twenty-six studies provided evidence for monitoring treatment in patients with gout.[1] The evidence was insufficient to correlate serum urate levels with outcomes. There was low level evidence that targeting a specific urate level reduces the risk of gout attacks.

Discontinuing Treatment for Acute and Chronic Gout

Only three studies were identified that discussed discontinuing gout treatment.[1] Moderate evidence supports the use of at least 8 weeks of NSAIDs or low dose colchicine prophylaxis for acute gout when starting ULT to reduce the risk of gout attacks. The evidence related to the most appropriate time to discontinue treatment is insufficient to draw firm conclusions.

Safety of Allopurinol Versus Other ULT

A systematic review and meta-analysis analyzed the safety of using allopurinol with ULT in patients with gout.[2] Patients included were at least 18 years of age and had a gout diagnosis as defined by the ACR (a) the presence of characteristic urate crystals in the joint fluid and/or b) a tophus proved to contain urate crystals by chemical or polarized light microscopic means, and/or c) the presence of clinical, laboratory, and X-ray phenomena outline by ACR) or evidence of urate crystals in the synovial fluid.[11] The primary outcomes studied were rates of adverse events and death. Seven randomized trials met inclusion criteria and were graded according to the Jadad scale and 4 systematic reviews were also included. Five studies were considered moderate in quality and 2 were high quality. Over 80% were males with a mean age 69 years. Comparisons to allopurinol (max dose 300 mg/day) included placebo, febuxostat (40-240 mg), probenecid and benzbromarone (not available in the US).[2] Abnormal liver function, diarrhea and rash were the most commonly reported adverse events. Overall most adverse events were mild to moderate in severity. In comparisons of allopurinol to febuxostat, the adverse events were similar between groups. Withdrawal rates were similar between groups with the most common reason being abnormal liver function tests (LFTs); however, high-dose febuxostat (120 mg) was associated with significantly higher withdrawal rates due to increased LFTs.[2] Cardiovascular events were rare: one event each were found with allopurinol, placebo and febuxostat 240 mg groups and 5 events in the febuxostat 80 mg and 120 mg groups. In a comparison of allopurinol to probenecid, higher rates of discontinuation were found in probenecid-treated patients compared to allopurinol (26% vs. 11%). Allopurinol was associated with a higher incidence rate and withdrawal due to rash compared to probenecid (7% vs. 3%); however, GI adverse reactions were more common with probenecid compared to allopurinol (23% vs. 7%). There was heterogeneity amongst the included studies, making comparisons of results difficult. Additionally, lower doses of allopurinol were used in most studies.[2]

New Guidelines:

EULAR 2016 Guideline on the Management of Gout

Updated EULAR guidelines on the management of gout were published this year.[3] Fifty-one references were analyzed and 11 recommendations were produced (Table 4). Evidence to support recommendations were based on *categories of evidence* and *strength of the recommendation*. The categories were graded from 1A to 4, with 1A being the highest level of evidence (meta-analysis of randomized trials) and 4 being expert opinion (Table 3). The category of evidence was used to develop the strength of the recommendations as outlined in Table 4. [3]

Table 3. EULAR Categories of Evidence

Category	Evidence
1A	From meta-analysis from randomized controlled trials
1B	From at least one randomized controlled trial
2A	From at least one controlled study without randomization
2B	From at least one type of quasi-experimental study
3	From descriptive studies, such as comparative studies, correlation studies or case-control studies
4	From expert committee reports or opinions and/or clinical experience of respected authorities

Table 4. EUAR Strength of Recommendation

Strength	Directly based on
A	Category I evidence
B	Category II evidence or extrapolated recommendations from category I evidence
C	Category III evidence or extrapolated recommendations from category I or II evidence
D	Category IV evidence or extrapolated recommendations from category II or III evidence

General overarching principles were that every patient should receive education on pathophysiology, treatments for gout, importance of SUA levels and comorbidities associated with gout. Additionally, the role of weight loss and diet (avoidance of alcohol, meat and seafood intake and sugar-sweetened drinks) and importance of exercise should be discussed.[3] It is advised that all patients with gout are screened for comorbidities and cardiovascular risk factors, such as: renal impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, obesity, hyperlipidemia, hypertension, diabetes and smoking. The recommendations and strength of the treatment recommendations are presented below (Table 5). Treatment algorithms for the management of acute gout and hyperuricemia are presented in Figures 1 and 2.

Table 5. 2016 EULAR Recommendations for the Treatment of Gout.[3]

Recommendation	Strength of Recommendation
1. Acute gout flares should be treated as soon as possible. Colchicine should be given as soon as possible, within 12 hours of symptom onset	D A
2. First-line options for acute gout flares: - Colchicine (except with severe renal impairment) and/or - NSAID (except with severe renal impairment); or - Oral corticosteroid; or - Articular aspiration and injection of corticosteroids	 A A A C
3. Frequent flares with contraindications to medications in #2 should be considered for IL-1 blockers - Recommendation based on evidence for canakinumab (not available in the US)	 A

- Evidence from anakinra	C
4. Acute gout prophylaxis is recommended in the first 6 months of ULT with colchicine (0.5-1 mg/day in patients with normal renal function). Use low dose NSAIDs as an alternative if not contraindicated.	B
5. ULT is indicated for patients with recurrent flares, tophi, urate arthropathy and/or renal stones. Patients at high risk should be offered ULT at time of diagnosis.	A
6. Patients taking ULT should have SUA levels maintained to < 6 mg/dL. Patients with severe gout should have target SUA levels of < 5 mg/dL (levels < 3 mg/dL long-term are not recommended).	C
7. ULT should be started at a low dose and titrated to SUA levels of < 6 mg/dL which should be maintained for life.	C
8. First-line option for ULT is allopurinol 100 mg/day (in patients with normal renal function), increasing dose by 100 mg every 2-4 weeks if needed. - If SUA target is not obtained with allopurinol then the patient should be switched to febuxostat **OR** - an uricosuric (probenecid or lesinurad) may be used alone or added to allopurinol.	A A B
9. Allopurinol doses should be adjusted in patients with renal impairment according to creatinine clearance.	C
10. Pegloticase injection is only indicated for patients who have not been able to obtain target SUA levels on other treatments, alone or in combination at maximal doses, and also have crystal-proven, severe debilitating chronic tophaceous gout and poor quality of life.	A
11. In patients on loop or thiazide diuretics who develop gout, alternative agents should be considered if possible.	C

Figure 1. Management of Gout Flares

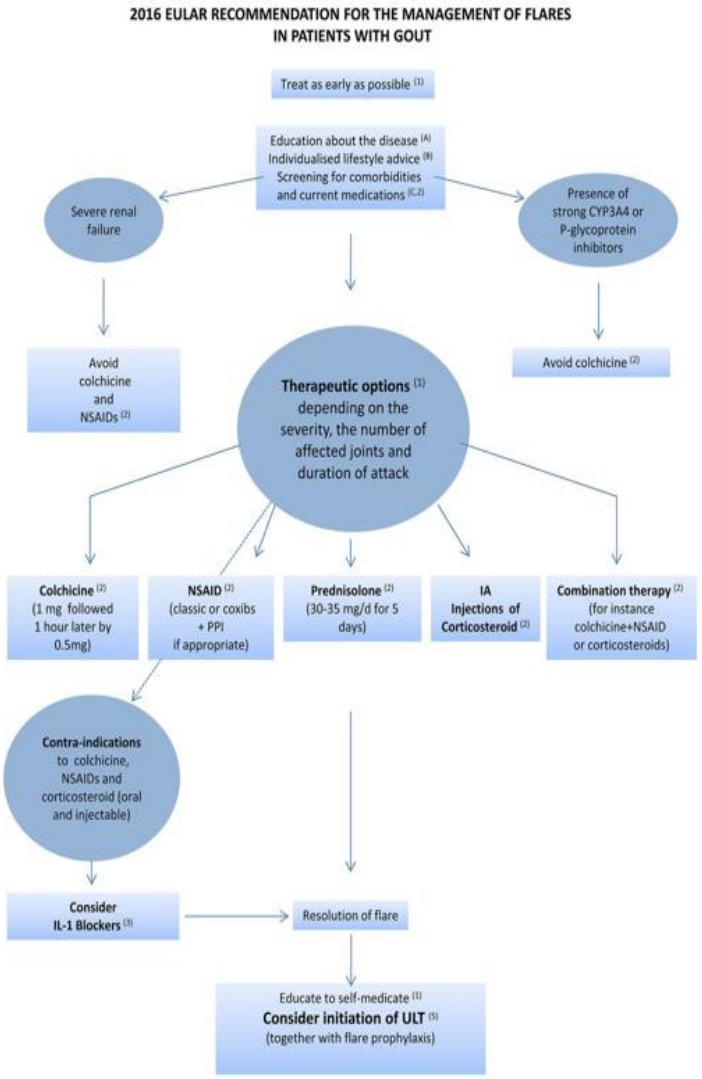
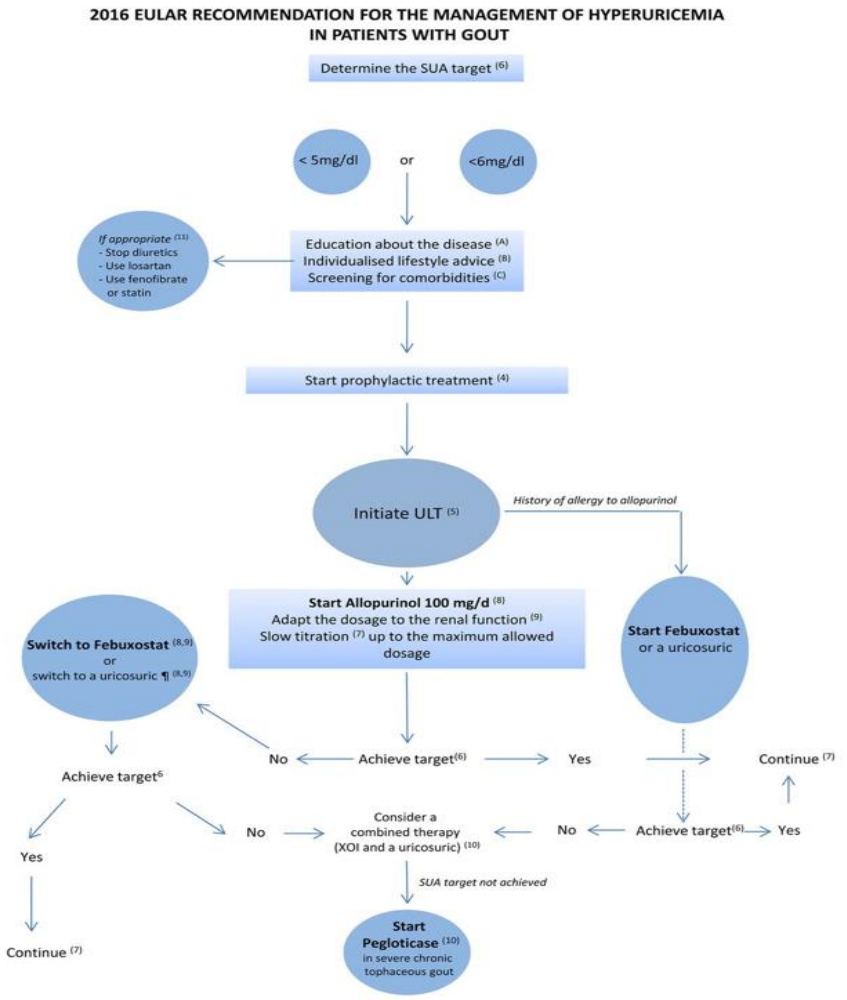


Figure 2. Management of Hyperuricemia



Richette P, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Ann Rheum Dis 2016. DOI: 10.1136/annrheumdis-2016-209707

Author: Sentena

Date: January 2017

American College of Physicians Management of Gout Guidelines

Guidelines for the management of acute and recurrent gout were published by the ACP.[4] The evidence was reviewed and evaluated according to ACP grading system. Recommendations were based on the AHRQ guidance presented above. Four recommendations were outlined by ACP.

1) Corticosteroids, NSAIDs or colchicine should be used for pain treatment in acute gout based on high strength of evidence.
    a. Corticosteroids are recommended as first-line because of safety and cost. NSAIDs are also very effective for pain associated with gout and moderate evidence found no difference between NSAIDs. Indomethacin is often thought as the first-line NSAID for gout but there is no evidence that it provides superior efficacy. Colchicine is an option but is more expensive than comparative treatments.
2) Low-dose colchicine is recommended when using colchicine for acute gout treatment based on moderate evidence.
    a. Colchicine 1.2 mg followed by 0.6 mg 1 hour later has been shown to be as effective for pain management as colchicine 1.2 mg followed by 0.6 mg/hour for 6 hours. Low-dose colchicine has also been shown to have a lower risk of GI adverse events compared to high-dose regimens.
3) Long-term ULT is not recommended for most patients after the first gout attack or for those with infrequent attacks based on moderate evidence.
    a. There is insufficient evidence to support the use of ULT long-term (>12 months) in patients with single or infrequent gout attacks.
4) Benefits, harms, costs and individual preferences should be discussed with patients before initiating ULT, including concomitant prophylaxis, based on moderate evidence.
    a. If ULT is appropriate, febuxostat (40 mg) and allopurinol (300 mg) offer similar serum urate lowering.
    b. There is insufficient evidence on the optimal duration of ULT; however, evidence supports a reduction in acute gout attacks after 1 year but not within the first 6 months.
    c. At least 8 weeks of prophylactic therapy with low-dose colchicine or NSAIDs has been shown to reduce the incidence of acute gout attacks in patients starting ULT.

New Safety Alerts:
No new safety alerts identified.

New Formulations or Indications:
No new formulations or indications identified.

Randomized Controlled Trials:
A total of 85 citations were manually reviewed from the literature search. After manual review, all trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical).

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	ALLOPURINOL	ALLOPURINOL	Y
ORAL	TABLET	ZYLOPRIM	ALLOPURINOL	Y
ORAL	TABLET	PROBENECID-COLCHICINE	COLCHICINE/PROBENECID	Y
ORAL	CAPSULE	COLCHICINE	COLCHICINE	N
ORAL	CAPSULE	MITIGARE	COLCHICINE	N
ORAL	TABLET	COLCHICINE	COLCHICINE	N
ORAL	TABLET	COLCRYS	COLCHICINE	N
ORAL	TABLET	ULORIC	FEBUXOSTAT	N
ORAL	TABLET	ZURAMPIC	LESINURAD	N
ORAL	TABLET	PROBENECID	PROBENECID	N

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) without Revisions** 1996 to September Week 3 2016

Search Strategy:

#	Searches	Results	Annotations
1	Allopurinol/	3272	
2	Colchicine/	4195	
3	Probenecid/	697	
4	Febuxostat/	258	
5	lesinurad.mp.	10	
6	1 or 2 or 3 or 4 or 5	8168	
7	limit 6 to (english language and humans and yr="2015 -Current")	323	
8	limit 7 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	85	

Author: Sentena

Date: January 2017

Agents for Gout

Goal(s):

- To provide evidenced-based step-therapy for the treatment of acute gout flares, prophylaxis of gout and chronic gout.

Length of Authorization:

Up to 12 months

Requires PA:

- Non-preferred drugs

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Will the provider switch to a preferred product? Note: Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee. Preferred products are available without a PA	**Yes:** Inform prescriber of covered alternatives in the class	**No:** Go to #3
3. Is the request for colchicine?	**Yes:** Go to #4	**No:** Go to #5
4. Has the patient tried and failed NSAID therapy or have contraindications to NSAIDs or is a candidate for combination therapy (i.e., multiple joint involvement and severe pain)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; recommend trial of NSAID

Approval Criteria		
5. Is the request for febuxostat and has the patient tried and failed allopurinol or have contraindications to allopurinol?	**Yes:** Approve for 12 months	**No:** Go to #6
6. Is the request for lesinurad?	**Yes:** Go to #7	**No:** Approve for 12 months
7. Is the patient concomitantly taking a xanthine oxidase inhibitor (e.g., allopurinol, fubuxostat)?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is the estimated CrCl < 45 mL/min?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for 12 months at a maximum daily dose of 200 mg

P&T/DUR Review: *1/17 (KS)*
Implementation: *TBD*