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Drug Class Update: Gout Agents

Date of Review: December 2020

Date of Last Review: January 2017
Dates of Literature Search: 11/01/2016 - 08/15/2020

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

Purpose for Class Update:
The purpose of this class update is to evaluate new evidence for the drugs used in the treatment of gout and update policy if necessary. Specifically, evidence for the role of colchicine in patients with cardiovascular disease (CV) will be reviewed and the evidence for the appropriateness of initiating non-steroidal anti-inflammatory drugs (NSAIDs) and colchicine concomitantly will be evaluated.

Summary of Prior Reviews and Current Policy:
- A drug class update was last preformed in January of 2017 resulting in no changes to the preferred drug list (PDL). High quality evidence supports the use of NSAIDs, colchicine, and systemic corticosteroids for the treatment of acute gout and reduction in serum urate (SU) levels with allopurinol and febuxostat. The use of low-dose colchicine is recommended over high-dose, as similar levels of pain relief have been demonstrated with a lower incidence of adverse reactions. For patients requiring urate lowering therapy (ULT) allopurinol is recommended first-line. Combination therapy with allopurinol and uricosurics is recommended for patients requiring additional therapy to obtain target SU levels. Long-term ULT is not recommended for a majority of patients after the initial attack or in patients with infrequent attacks.
- Allopurinol and a combination product of probenecid/colchicine are preferred therapies in the class. All other gout treatments are subject to prior authorization (PA) criteria.

Research Questions:
1. What is the comparative evidence of efficacy for drug therapies used in the management of gout based on important outcomes such gout flares, SU levels and pain?
2. What is the evidence for harms associated with therapies for the treatment of gout?
3. 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?
4. What is the evidence for the use of colchicine in cardiovascular disease?
5. Is there evidence for the use of NSAIDs and colchicine concomitantly?

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Conclusions:

- Two systematic reviews, 4 guidelines and 2 randomized controlled trials (RCT) are included in this evidence review. There was no new evidence for the use of NSAIDs, colchicine, systemic corticosteroids, allopurinol, febuxostat and probenecid for the treatment of gout.

CARDIOVASCULAR

- There is evidence to recommend colchicine for prevention of CV outcomes in patients at high risk for CV events and for those with a recent myocardial infarction (MI) supported by evidence from one systematic review and 2 randomized controlled trials.
    - A Cochrane review found colchicine was not significantly different from controls for mortality (all-cause and CV). Myocardial infarction, mostly non-fatal, was reduced in adult patients, compared to placebo and all other types of comparators (IFN-c 1b, peg-interferon-alpha, aspirin, prednisone, ursodeoxycholic acid, methotrexate, melphalan, dimethyl sulfoxide, and standard care for chronic liver disease [diuretics, beta-blockers, ursodeoxycholic acid]), based on moderate strength of evidence, 12 per 1000 patients vs. 58 per 1000 patients (relative risk [RR] 0.20; 95% confidence interval [CI], 0.07 to 0.57).[1]
    - A good quality, double-blind, placebo-controlled trial in patients with a history of chronic coronary disease found colchicine to reduce the composite primary endpoint of CV death, spontaneous MI, ischemic stroke or ischemic-driven coronary revascularization by 6.8% compared to 9.6% in the placebo group (absolute risk reduction [ARR] 2.8%/ number needed to treat [NNT] 36) (moderate strength of evidence).[2]
    - A good quality trial in patients with a recent MI found colchicine to reduce the composite end-point of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization by 5.5% in the colchicine group compared to 7.1% in the placebo group (ARR 1.6% /NNT 63) (moderate strength of evidence).[3]
- There is moderate strength of evidence that colchicine, when combined with a NSAID, is more effective than an NSAID alone at reducing recurrent pericarditis (ARR 23%/NNT 5). Acute pericarditis was reduced with colchicine (in combination with an NSAID) compared to an NSAID alone based on moderate strength of evidence (ARR 22% and NNT of 5).[4]

GOUT

- Evidence from the following guideline updates support the current policy for gout treatments: 2016 American College of Physicians (ACP) guideline, 2017 guideline from the British Society for Rheumatology (BSR) and the 2020 American College of Rheumatology (ACR) guideline on gout management.
- There is a paucity of evidence to guide the use of combination anti-inflammatory therapies in the acute treatment of gout. The BSR recommends the use of an NSAID with a steroid (oral or intra-articular) or colchicine in patients with acute gout who have an insufficient response to monotherapy, which is based on expert opinion due to insufficient evidence.[5]

BEHÇET'S SYNDROME

- A 2018 recommendation from the European League Against Rheumatism (EULAR) on the management of Behçet's Syndrome (BS) recommends the use of colchicine, with or without NSAIDs, for mucocutaneous and arthritic manifestations of BS (high strength of evidence).

Recommendations:

- No changes to the PDL are warranted based on new clinical evidence presented in this review.
- Recommend amending the PA criteria to allow for colchicine use in patients with pericarditis and BS. Permit short-term use of colchicine without a PA.
- After evaluation of costs in executive session, colchicine tablets were preferred.

Background:

Gout is the most common form of inflammatory arthritis.[6] The pathophysiology of gout is a result of 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.[7] The 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.[7] The American College of Physicians (ACP) recommends synovial fluid analysis in patients with acute gout if diagnostic testing is indicated.[8]

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.[8] Asymptomatic hyperuricemia can also occur; however, there is no evidence to support treatment as a preventative strategy for progression to symptomatic gout.[8] 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.[9] 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: pain, serum and/or uric acid levels, gout attacks, development of tophi, progression from acute to chronic gout and quality of life.

Risk factors for the development of gout include obesity, excessive alcohol intake, dietary factors, medications that increase uric acid levels and chronic kidney disease.[10] It is generally recommended that non-pharmacological therapy, in the way of lifestyle factors, be modified to manage gout, in addition to pharmacotherapy. 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.[6] Patients are also encouraged to minimize impact of comorbidities by optimizing weight, regular exercise, dietary modifications, minimizing alcohol consumption, and treatment of underlying CV risk factors.[10] Vitamin C supplementation has been suggested but there is no evidence to support its use in the management of gout.[11]

Selection of gout therapies is dependent on the diagnosis of acute or chronic gout (Table 1).[6,10] Treatment for acute gout should be initiated within 24 hours of the onset of the attack. The ACR recommends treatment based on severity of pain and the number of joints involved.[12] 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 when monotherapy is insufficient. Combination options are: 1) NSAIDs and colchicine; 2) oral corticosteroids and colchicine; or 3) intra-articular steroids and one of the other oral treatment options.[12] Combination therapy for initial therapy is based on off consensus opinion due to lack of high-quality evidence. In severe refractory cases of gout, use of a biologic interleukin-1 (IL-1) inhibitor can be considered based on moderate strength of evidence.[11] High strength of evidence supports the use of adrenocorticotropic hormone (ACTH) subcutaneous injections as an option in patients who are not able to take medications by mouth.[12,11]

Management of chronic gout focuses on urate reduction through ULT (**Table 1**).[5,13] 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.[6] 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),

specifically allopurinol followed by febuxostat, are recommended as first-line pharmacological treatment options. Alternative pharmacological options are uricosurics (probenecid).[12] Combination therapy with a XOI and probenecid are recommended if there is an insufficient response to XOI monotherapy.[6] 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.[6] Low dose colchicine (0.6 mg twice daily) or NSAIDs are recommended first-line for prophylaxis. 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.

Table 1. Treatments used for the Management of Gout[5,13]

Drug	Mechanism of Action
Acute Gout Management	
NSAIDs†	Anti-inflammatory
Corticosteroids (intraarticular or oral†)	Anti-inflammatory
Colchicine†	Anti-microtubule disrupting agent/anti-inflammatory
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 increased excretion
Abbreviations: NSAID – non-steroidal anti-inflammatory drugs Key: † Also recommended for gout prophylaxis	

Off-label Colchicine Uses

There is limited evidence for the use of colchicine in the treatment of pericarditis. Pericarditis is an inflammatory condition of the pericardium, a membrane that surrounds the heart. Recurrent pericarditis causes severe chest pain and is a common complication of acute pericarditis. The underlying etiology of pericarditis is often viral or idiopathic. European Society of Cardiology (ESC) recommends combination treatment with NSAIDs (for approximately two weeks) and colchicine (for approximately 3 months for acute pericarditis and at least 6 months for recurrent pericarditis) for the treatment of acute and recurrent pericarditis.[14] Glucocorticoids can be used as an alternative if patients have contraindications to NSAIDs.

Colchicine is used off-label for the treating BS. Behçet's Syndrome is an inflammatory syndrome that often presents with recurrent oral aphthous ulcers in addition to systemic manifestations, such as joint involvement and arthritis.[15] BS has a relapsing remitting component which is most commonly treated with anti-inflammatories to suppress inflammatory exacerbations. Standards of care include the use of colchicine, 1-2 mg/day (divided) as a first-line treatment option for recurrent oral or genital ulcers and for arthritic manifestations, with or without NSAIDs.[15]

There are approximately 6,000 patients in the Fee-for-Service population with the diagnosis of gout and only about 70 with BS. The overall costs for the class do not represent a large expenditure for the Oregon Health Plan (OHP). PDL compliance is around 80%.

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), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, 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.

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:

Colchicine Use for Cardiovascular Indications

Cochrane – Colchicine for Prevention of Cardiovascular Events
A 2016 Cochrane review evaluated the evidence for the use of the anti-inflammatory colchicine on prevention of CV outcomes in adult patients, especially patients with high CV risk.[1] Recent studies have noted a benefit with low-dose colchicine on CV outcomes; however, previous evidence has not demonstrated a CV benefit. Thirty-nine trials (n=4,992) were included in the analysis. Most trials were small, single-center studies with placebo comparators. Active treatment comparisons consisted of the following: IFN-c 1b, peg-interferon-alpha, aspirin, prednisone, methotrexate, melphalan, dimethyl sulfoxide, and standard care for chronic liver disease (diuretics, beta-blockers, ursodeoxycholic acid). Four trials focused specifically on the use of colchicine in the CV setting (e.g., in patients with diabetes, undergoing stent implantation, heart failure [HF], coronary artery disease [CAD] or after angioplasty). The most commonly studied colchicine dose used in the 69% of the trials was 1 mg/day or less and 1.2 mg/day in the remaining trials. CV endpoints were not the primary endpoints of most of the included trials. The risk of bias was often considered unclear due to trial methodology used in older trials. The primary outcomes of interest were all-cause mortality, MI, and adverse events.

There is moderate strength of evidence that colchicine had no effect on all-cause mortality compared to any control treatment over a period of 0.5 to 14 years, 182 per 1000 patients vs. 193 per 1000 patients (RR 0.94; 95% CI, 0.82 to 1.09).[1] In a subgroup analysis of patients with high CV risk (secondary prevention of CV disease events, established coronary heart disease) there also was no difference in all-cause mortality (RR 0.54; 95% CI, 0.26 to 1.14) (moderate strength of evidence). Moderate strength of evidence demonstrated that there was also no significant effect of colchicine on CV mortality compared to any control over a period of 0.5 -14 years (RR 0.34; 95% CI, 0.09 to 1.21).[1] Findings were consistent for CV mortality in patients with high CV risk, based on low strength of evidence (RR 0.25; 95% CI, 0.02 to 2.66).[1] There was no difference in findings between colchicine and type of control treatment used. Further research is needed to establish whether colchicine reduces CVD mortality.

There was moderate strength of evidence of a benefit with colchicine, compared to any control, on reducing the risk of MI (mostly non-fatal) over a 3 year period. The incidence of MI was 12 per 1000 patients with colchicine vs. 58 per 1000 patients with controls (RR 0.20; 95% CI, 0.07 to 0.57). In a subgroup analysis, patients at high CV risk had 18 MIs per 1000 patients with colchicine vs 72 per 1000 patients in the control group (RR 0.20; 95% CI, 0.07 to 0.57).[1] Evidence on MI risk was mostly from a single study. Evidence was insufficient for meaningful conclusions to be drawn from data on HF risk and stroke risk.

In summary, there is CV benefit, especially on reducing the risk of MI, with the use of colchicine; however, additional evidence is needed to confirm treatment benefit (See randomized clinical trials presented below). Evidence was downgraded due to imprecision of trial results and missing outcome data for many of the studies.

Cochrane – Colchicine for Pericarditis

There is some evidence to suggest that colchicine is effective in preventing reoccurring pericarditis.[4] A Cochrane review searched evidence up to August 2014 for evidence of effectiveness of colchicine (0.5 mg twice daily) in adult patients with acute or recurrent pericarditis. Four trials met inclusion criteria which included 564 participants. Seventy-seven percent of patients had idiopathic pericarditis. All trials compared colchicine to NSAIDs (e.g., ibuprofen, aspirin, or indomethacin). The primary outcome was time to pericarditis recurrence. Pericarditis was defined as chest pain with (ECG changes +/- echocardiographic changes +/- raised inflammatory markers).

Recurrent pericarditis was reduced in patients treated with colchicine (combined with NSAIDs) compared to NSAIDs alone in trials with a median duration of 18 months based on moderate strength of evidence (HR 0.37; 95% CI, 0.24 to 0.58/NNT 4).[4] Recurrent pericarditis, was reduced with colchicine (in combination with an NSAID) compared to an NSAID alone at 6 months, 137 cases per 1000 patients vs. 490 per 1000 patients (RR 0.28; 95% CI, 0.17 to 0.47) (moderate strength of evidence).[4] At 12 months the reduction in pericarditis risk was maintained (RR 0.36; 95% CI, 0.23 to 0.56) and also at 18 months (RR 0.38; 95% CI, 0.25 to 0.58) (moderate strength of evidence for both).[4] At 18 months the ARR between groups was 23% with an NNT of 5.[4]

There was moderate strength of evidence that colchicine (in combination with NSAIDs) reduced reoccurring acute pericarditis compared to NSAIDs alone with a HR of 0.40 (95% CI, 0.27 to 0.61).[4] Colchicine (combined with an NSAID) compared to an NSAID alone, reduced the recurrence rate of pericarditis in patients with acute pericarditis at 6 months based on moderate strength of evidence (RR 0.36; 95% CI, 0.23 to 0.58).[4] Moderate strength of evidence demonstrated similar results at 12 months (RR 0.40; 95% CI, 0.26 to 0.61) and at 18 months (RR 0.41; 95% CI, 0.28 to 0.61).[4] The ARR between groups was 22% with an NNT of 5.[4]

There was low quality of evidence that colchicine (in combination with an NSAID) provided more symptom relief of pericarditis compared to NSAIDs alone (RR 1.40; 95% CI, 1.26 to 1.56).[4] There was low strength of evidence that adverse effects were not different between groups.

In summary, colchicine (in combination with an NSAID) was more effective than NSAIDs alone in preventing pericarditis recurrence in patients with reoccurring pericarditis or in acute pericarditis. There were only a few participants enrolled in the trials with resistant multiple recurrences, limiting external validity to this population.

Randomized Controlled Trials:
A total of ninety-one citations were manually reviewed from the initial literature search. After further review, eighty-nine citations were excluded because of wrong study design (eg, observational), or outcome studied (eg, non-clinical). Two trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

There is evidence for the use of colchicine in patients with coronary disease and recent MI from two good quality, double-blind, randomized, placebo controlled trials in comparing colchicine 0.5 mg daily to placebo (**Table 2**).[2,3] In first trial, patients had a history of chronic coronary disease and a majority were at least 24 months from having an acute coronary procedure. Patients were optimized on maintenance medications for chronic coronary disease (e.g., statin and lipid lowering agents) and baseline characteristics were well-matched. Incidence rates, based on the composite primary endpoint of CV death, spontaneous (non-procedural) myocardial infarction, ischemic stroke or ischemic-driven coronary revascularization were reduced with colchicine with incidence rates of 2.5 events per 100 person-years compared to 3.6 events per 100 person-years with placebo (**Table 2**).[2] Reductions in composite endpoint was driven by MI events, 3.0% in colchicine treated patients compared to 4.2% in patients treated with placebo (P=0.01/ARR 1.2%/NNT 84). Death from any cause or CV death was not different between groups.

In the second trial, the use of colchicine compared to placebo was studied in adult patients with a recent history of MI (within 30 days before enrollment, mean of 13.5 days), had completed any planned percutaneous revascularization procedures and were treated according to national guidelines.[3] Patients with heart failure (HF), a left ventricular ejection fraction less than 35% or stroke within the previous 3 months were excluded. A majority of patients were on aspirin, a different antiplatelet agent and statin. The primary endpoint, composite of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization, was reduced in patients taking colchicine compared to placebo, ARR 1.6%/NNT 63 (**Table 2**).[3] The composite endpoint was driven by MI events, 3.8% in patients treated with colchicine compared to 4.1% treated with placebo (HR 0.91; 95% CI, 0.68 to 1.21; P>0.05).[3] All-cause death and death from CV causes was not different between groups.

Table 2. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Nidorf, et al[2] Phase 3, DB, RCT 28.6 months	Colchicine 0.5 mg once daily Vs. Placebo once daily	Adult patients (35-82 years) with chronic coronary disease (n=5522)	Composite of CV death, spontaneous (non-procedural) myocardial infarction, ischemic stroke or ischemic-driven coronary revascularization	Colchicine: 187 (6.8%) Placebo: 264 (9.6%) HR 0.69 (95% CI, 0.57 to 0.83) P<0.001 ARR 2.8% / NNT 36
Tardif, et al[3] Phase 3, DB, RCT 22.6 months	Colchicine 0.5 mg daily Vs. Placebo daily	Adult patients with MI within 30 days of enrollment, had completed planned percutaneous	Composite end-point of death from CV causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization	Colchicine: 131 (5.5%) Placebo: 170 (7.1%) HR 0.77 (95% CI, 0.61 to 0.96) P= 0.02 ARR 1.6% / NNT 63

		revascularization procedures and were treated according to national guidelines, including intensive use of statins (n=4745)		

Abbreviations: ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; DB = Double-blind; HR = hazard ratio; MI = myocardial infarction; NNT = number needed to treat; RCT = randomized clinical trial

After review, 11 systematic reviews were excluded due to poor quality (e.g, indirect network-meta analyses or failure to meet AMSTAR criteria), wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[16–20,20–26]

New Guidelines:
High Quality Guidelines:

GOUT

American College of Rheumatology – Management of Gout
The 2012 guidance of the management of gout was updated by the ACR in 2020.[11] The objective of the guidance is to provide recommendations on the management of gout as it pertains to: ULT, gout flare management and lifestyle and other medication recommendations. Recommendations are applicable to patients with gout and those with asymptomatic hyperuricemia ($\geq$ 6.8 mg/dl with no prior gout flares or subcutaneous tophi).[11] Guideline methodology was clearly described and 26% of the authors had declared conflicts of interest. Network meta-analyses, with their inherent limitations, were used to determine the effects of starting ULT versus no ULT and for the use of different anti-inflammatory agents in the management of gout flares.

The ACR provided pharmacological recommendations for the management of gout, divided into 4 categories: indications for pharmacological ULT, choice of initial ULT, recommendations pertaining to specific ULT medications and gout flare management.[11] Recommendations are outlined in **Table 3**. For patients that are appropriate candidates, and currently taking ULT, dose titration should be guided by SU values (strongly recommended; moderate strength of evidence). A SU goal and attainment should be < 6 mg/dl when on ULT. Indefinitely using ULT is recommend over stopping it based on very low quality evidence and a conditional recommendation. Guidance on switching ULT is outlined in **Table 4**.

For specific patient subgroups, alternative ULT recommendations are in place. For patients who are of Southeast Asian decent or African America, an HLA-B*5801 test should be conducted before initiating allopurinol therapy but not for other patient populations (very low strength of evidence).[11] Desensitization is

recommended for patients with a prior allergic reaction to allopurinol who cannot be treated with other oral ULTs (very low strength of evidence). Moderate quality evidence suggests that patients with a history of CVD or a new CV event that are taking febuxostat should be switched to an alternative ULT if appropriate. Urine uric acid concentrations are not recommended for patients taking uricosurics, or considering taking uricosurics (very low quality of evidence).[11]

Table 3. ACR Management of Gout Recommendations[11]

Recommendations	Strength of Evidence	Strength of Recommendation
Indications for ULT		
1. ULT should be initiated in patients with 1 or more subcutaneous tophi	High	Strong
2. Patients with radiographic damage attributable to gout should have ULT initiated	Moderate	Strong
3. Patients that experience frequent gout flares (> 2/year) should have ULT initiated	High	Strong
4. For patients with a history of flares (>1) but experience infrequent flares (<2/year), ULT is recommended	Moderate	Conditional
5. Patients with their first flare **should not** receive ULT, except for patients described below	Moderate	Conditional
A. Patients with their first flare and CKD stage ≥3, SU >9 mg/dl, or urolithiasis	Very low	Conditional
6. For patients with asymptomatic hyperuricemia (SU >6.8 mg/dl), with no prior gout flares or subcutaneous tophi, ULT **should not** be initiated	High	Conditional
Choice of Initial ULT in Patients with Gout		
7. Allopurinol is recommended over other ULTs as the first-line therapy (including patients with CKD ≥3)	Moderate	Strong
8. XOIs are recommended over probenecid for patients CKD ≥ 3	Moderate	Strong
9. Initiating allopurinol and febuxostat should be done at low doses with the intent of dose titration (e.g., ≤ 100 mg/day for allopurinol [lower in patients with CKD] or ≤ 40 mg/day for febuxostat)	Moderate	Strong
10. Probenecid should be started at a lower dose (e.g., 500 mg once or twice daily) with dose titration	Moderate	Conditional
11. Concomitant anti-inflammatory* (e.g., colchicine, NSAIDs, prednisone/prednisolone) prophylaxis should be initiated over no prophylaxis	Moderate	Strong
12. Prophylaxis should be continued for 3-6 months rather than < 3 months†	Moderate	Strong
13. If ULT is indicated during a gout flare, it is recommended that ULT be initiated during the flare instead of waiting till the flare has resolved	Moderate	Conditional
14. Pegloticase **should not** be used as a first-line therapy	Moderate	Strong
Gout Flare Management		
15. Patients with gout flares should be managed with colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular)* first-line versus IL-1 inhibitors or ACTH	High	Strong
16. If colchicine is initiated, low-dose (0.6 mg twice daily) versus high-dose should be used	Moderate	Strong

17. Patients with a gout flare who are unable to tolerate, or therapies are contradicted, an IL-1 inhibitor is recommended over no therapy	Moderate	Conditional
18. Patients who are unable to tolerate oral therapy should receive glucocorticoids (intramuscular, intravenous, or intraarticular) over IL -1 inhibitors or ACTH	High	Strong
19. Topical ice can be used during a gout flare if desired as an adjuvant treatment	Low	Conditional
Abbreviations: ACTH - adrenocorticotropic hormone; CKD – chronic kidney disease; IL-1 – interleukin type 1; NSAIDs – non-steroidal anti-inflammatory drugs; SU – serum urate; ULT – urate lowering therapy; XOI – xanthine oxidase inhibitors Key: * Specific patient characteristics should guide anti-inflammatory choice, † Continual evaluation is warranted and continued prophylaxis may be needed if patient continues to have flares		

Table 4. ACR Guidance for Switching to a New ULT[11]

Recommendation	Strength of Evidence	Strength of Recommendation
1. For patients on first maximally tolerated dose XOI monotherapy or FDA-indicated dose and are not at SU target and/or have continuation of frequent gout flares or nonresolving subcutaneous tophi it is recommended that the patient be switched to and alternative XOI over adding a uricosuric therapy	Very low	Conditional
2. Patients who have not achieved SU targets on an XOI, uricosurics and other interventions, with gout and frequent gout flares, or nonresolving subcutaneous tophi, pegloticase is recommended over continuing current ULT	Moderate	Strong
3. Continuing current ULT therapy versus switching to pegloticase is recommended for the following patients with gout: - XOI, uricosurics and other interventions have failed to lower SU to target AND - Have infrequent gout flares (< 2 flares/year) AND - No tophi	Moderate	Strong
Abbreviations: FDA – Food and Drug Administration; SU – serum urate; ULT – urate lowering therapy; XOI – xanthine oxidase inhibitors		

<u>American College of Physicians – Management of Acute and Recurrent Gout</u>

A clinical practice guideline on gout management in adults was published from ACP in 2020 to assist primary care practitioners.[9] The guidance is based off a recent systematic review and meta-analysis performed and funded by Agency for Healthcare Research and Quality (AHRQ). Twenty-eight studies provided evidence for the pharmacological therapies used in the treatment of gout.

The treatment recommendations are described in **Table 5**.[9] Acute gout pharmacotherapy recommendations pertain to colchicine, NSAIDs and corticosteroids. Recommendations for colchicine were based on high-quality evidence that colchicine reduces pain. Moderate-quality evidence found low-dose colchicine (1.2 mg initial dose followed by 0.6 mg in 1 hour) are as effective as higher colchicine doses (1.2 mg initially followed by 0.6 mg/hr for 6 hours). Low-dose colchicine

provided similar pain relief to that of high-dose with a lower incidence of gastrointestinal adverse reactions.[9] Evidence for NSAIDs supported their use in gout as a pain reliever and for prevention of gout flares during urate-lowering therapy. The most common adverse reaction associated with NSAIDs are gastrointestinal, ranging from dyspepsia to bleeding ulcers. The recommendation for corticosteroids ability to reduce pain in patients with acute gout comes from high-quality indirect evidence. Finding for corticosteroids are similar to NSAIDs in time to resolution of symptoms, clinical joint status, or pain reduction.

Evidence demonstrating reduction in SU results from urate lowering therapy (allopurinol and febuxostat) came from 4 RCTs.[9] Lowering of SU was not associated with a reduction in gout attacks within the first 6 months of treatment; however, observational and retrospective cohort studies have shown lower SU levels results in in fewer gout flares. In a comparative effectiveness analysis between allopurinol and high-dose febuxostat (120 mg or 240 mg a day), febuxostat had a higher incidence of gout flares compared to patients treated with allopurinol (100-300 mg a day).[9] Febuxostat (40 mg daily) and allopurinol (300 mg daily) lowered SU levels to the same degree, while febuxostat 80 mg daily was more effective than allopurinol.[9] Lower doses of febuxostat (40 mg and 80 mg a day) and allopurinol had similar efficacy in the number of gout flares. Rash is the most common adverse reaction associated with allopurinol and abdominal pain, diarrhea and musculoskeletal pain with febuxostat. Prophylaxis with low-dose colchicine (0.6 mg twice daily) or NSAIDs demonstrated a reduced risk for gout attacks in patients starting ULT with durations of therapy beyond 8 weeks being more effective than shorter durations of treatment. There is insufficient evidence to recommend treating patients to a target SU level or for specific criteria to guide ULT discontinuation.[9]

Table 5. ACP Guideline Recommendations for Gout Management[9]

Recommendation	Strength of Recommendation	Quality of Evidence
1. Corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), or colchicine should be used to treat patients with acute gout	Strong	High
2. Low-dose colchicine (0.6 mg twice daily) should be used to treat acute gout	Strong	Moderate
3. Long-term urate lowering therapy is not recommended for most patients after a first gout attack or in patients with infrequent attacks.	Strong	Moderate
4. The benefits, harms, costs, and individual preferences should be discussed with patients before initiating urate-lowering therapy, including concomitant prophylaxis, in patient with recurrent gout attacks.	Strong	Moderate

<u>British Society for Rheumatology – Management of Gout</u>

The BSR updated guidelines for the management of gout in adults in 2017. This guidance updates to the 2007 recommendations.[5] The guideline is accredited by the National Institute for Health and Care Excellence (NICE) meeting high-quality methodology standards. Literature was searched from 1974 to June 2015. Level of evidence was graded as described in **Table 6**. Recommendations pertaining to pharmacological management are discussed below. Treatment of acute gout attacks should be treated upon presentation, with an emphasis on continuing established ULT if appropriate.

Table 6. British Society of Rheumatology Level of Evidence Determination[5]

Level of Evidence
1a) meta-analysis of randomized controlled trials
1b) at least one randomized controlled trial

IIa) at least one well-designed controlled study without randomization
IIb) at least one well-designed quasi-experimental study
III) at least one non-experimental descriptive study (e.g., comparative correlation or case-control study)
IV) expert committee reports, opinions and/or experience of respective authorities

Acute Gout

Recommendations for the treatment of acute gout are consistent with other guidelines. Colchicine (0.5 mg once or twice daily) or NSAIDs, at maximum dose, are recommended first-line if there are no contraindications (Ia level of evidence [LoE]). Patients taking NSAIDs or cyclooxygenase-2 inhibitors should also take a gastroprotective agent. An alternative to colchicine and NSAIDs includes joint aspiration and injection of a corticosteroid, especially in monoarticular gout (IV LoE). Combination therapy for acute gout with NSAIDs with corticosteroids or colchicine can be used when the response to monotherapy is suboptimal (V LoE). Patients who do not respond to standard treatment of acute gout may be considered for IL-1 inhibitors (canakinumab, anakinra and rilonacept); however, this therapy recommendation is not approved by the National Institute for Health and Care Excellence (NICE) due to uncertainty of efficacy and safety evidence.

Urate-lowering Therapies

In contrast to the ACR recommendations, the BSR recommends that all patients who have a diagnosis of gout should be offered ULT. Urate lowering therapy should be highly considered for patients who have 2 or more gout attacks in 12 months, tophi, chronic gouty arthritis, joint damage, renal impairment (estimate glomerular filtration rate of 60 ml/min or less), history of urolithiasis, diuretic therapy use, or primary gout starting at a young age (Ia LoE for all except urolithiasis [III LoE] and diuretics and young age [IV LoE]). The guideline recommends discussing ULT with the patients when inflammation is under control and without pain; however, in patients with frequent attacks, it may be appropriate to initiate ULT before resolution of inflammation (IV LoE). The BSR recommends target a SU level of less than 300 µmol/l with ULT to prevent the formation of further urate crystals. A higher SU level can be targeted (360 µmol/l) after tophi have resolved and the patient is symptom free (III and IV LoE). First-line ULT recommendation is for allopurinol (50-100 mg daily) titrated every 4 weeks by a 100 mg until target SU has been reached (Ib LoE). Patients with renal impairment should be have doses titrated by 50 mg every 4 weeks (III LoE). Febuxostat 80 mg daily is a second-line option for ULT, that can be titrated to 120 mg daily if needed (Ia LoE). If XOIs are not tolerated, an alternative therapy option is a uricosuric agent (e.g., probenecid 500-2000 mg daily) (Ia LoE). Patients who have hyperlipidemia and hypertension may be candidates for losartan or fenofibrate, as they have weak uricosuric properties, as does Vitamin C supplements (III LoE). Patients who do not reach SU targets can be given combination therapy with an uricosuric agent and XOI (III LoE).

Prophylaxis

For prophylaxis against acute gout attacks, when ULT is initiated or titrated, colchicine (0.5 mg daily or twice daily) should be offered (Ib LoE). An NSAID, with a gastroprotectant, can be offered as an alternative in patients who are not able to tolerate colchicine (Ib LoE).

Special Populations

Renal Insufficiency: In acute gout, the dose of colchicine should be reduced in patients with an estimated glomerular filtration rate (eGFR) of 10-50 ml/min/1.73 m^2 and not used if the eGFR is 10 ml/min/1.73 m^2 or less. NSAIDs are also not recommended in patients with moderate to severe renal impairment and the patient should be considered a candidate for corticosteroid use.

Severe Refractory Tophaceous Gout: A rheumatologist should be consulted if a patient has severe symptomatic tophaceous gout in which SU cannot be controlled by ULT as monotherapy or in combination therapy. Pegloticase may be an option for these patients, although not approved by NICE.

Pregnancy: NSAIDs can be used in the second trimester in patients who are pregnant with gout. Steroids can be an alternative option. There is no data on allopurinol or febuxostat in pregnancy and they should not be used. Probenecid has been used as an antibiotic in pregnant patients without adverse effects.

BEHÇET'S SYNDROME

EULAR – Management of Behçet's Syndrome

EULAR provided recommendations for the management of BS in a 2018 recommendation statement.[27] EULAR followed the Appraisal of Guidelines Research and Evaluation instrument for development. Endorsed recommendations met inclusion criteria according to the AGREE tool as being high-quality guidance. Recommendations are graded from A-D, A is based on category I evidence and D corresponds to category IV evidence.

Recommendations for the management of BS, as they pertain to medications also used for gout, are presented (**Table 7**).[27] The anti-inflammatory, colchicine, has a role in BS because of the relapsing and remitting course of BS caused by inflammatory exacerbations, which if not managed can lead to irreversible organ damage. The use of colchicine 1-2 mg daily for mucocutaneous lesions and arthritis was used in trials. Improvement in mucocutaneous lesions, complete remission in mucocutaneous lesions and arthritis, and improvement in the Iranian Behçet's Disease Dynamic Activity Measure (IBDDAM) score provided evidence for the use of colchicine in BS. [28]

Table 7. EULAR Recommendations for the Management of Behçet's Syndrome Pertaining to Colchicine Use[27]

Recommendation	Level of Evidence	Strength of Recommendation
Mucocutaneous Involvement		
Colchicine should be used first-line for the prevention of recurrent mucocutaneous lesions, especially for erythema nodosum or genital ulcer	IB	A
Joint Involvement		
Colchicine is recommended first-line for the treatment of BS patients with acute arthritis	IB	A
Abbreviations: BS - Behçet's Syndrome		

After review, one guideline was excluded due to poor quality.[13]

New Formulations or Indications:
None identified.

New FDA Safety Alerts:

Table 8. Description of new FDA Safety Alerts

Generic Name	Brand Name	Month / Year of Change	Location of Change (Boxed Warning, Warnings, CI)	Addition or Change and Mitigation Principles (if applicable)
Allopurinol[29]	ALOPRIM	8/28/2020	Warnings	Serious and fatal dermatological reactions, including toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported in approximately 5 in 10,000 patients (0.05%). Exfoliative, urticarial and purpuric lesions; generalized vasculitis and irreversible hepatotoxicity have also been reported. Patients with the HLA-B*58:01 allele are at higher risk of allopurinol hypersensitivity syndrome (AHS). Consider testing for the allele in genetically at-risk populations. Do not use allopurinol in patients with the HLA-B*58:01 allele unless the benefit clearly outweighs the risk. Patients with renal impairment, especially in those receiving thiazide diuretics may be at increased risk of hypersensitivity reactions.
Febuxostat[30]	ULORIC	2/21/2019	Boxed warning	Increased risk of cardiovascular death in patients with gout and established cardiovascular disease taking febuxostat compared to those taking allopurinol

References:

1. Hemkens LG, Ewald H, Gloy VL, et al. Cardiovascular effects and safety of long-term colchicine treatment: Cochrane review and meta-analysis. *Heart*. 2016;102(8):590-596. doi:10.1136/heartjnl-2015-308542
2. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in Patients with Chronic Coronary Disease. *N Engl J Med*. Published online August 31, 2020. doi:10.1056/NEJMoa2021372
3. Tardif J-C, Kouz S, Waters DD, et al. Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction. *N Engl J Med*. 2019;381(26):2497-2505. doi:10.1056/NEJMoa1912388
4. Alabed S, Cabello JB, Irving GJ, et al. Colchicine for pericarditis. Cochrane Database of Systematic Reviews 2014. Issue 8, Art.No.:CD10652. DOI: 10.1002/14651858.CD010652.pub2. Accessed August 19, 2020. https://www-cochranelibrary-com.liboff.ohsu.edu/cdsr/doi/10.1002/14651858.CD010652.pub2/full?highlightAbstract=colchicin%7Ccolchicine%7Cpericard%7Cpericarditis

5. Hui M, Carr A, Cameron S, et al. The British Society for Rheumatology Guideline for the Managment of Gout. Rheumatology. 2017;56:e1-e20.
6. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res (Hoboken)*. 2012;64(10):1431-1446. doi:10.1002/acr.21772
7. Neogi T, Jansen TLTA, Dalbeth N, et al. 2015 Gout classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis*. 2015;74(10):1789-1798. doi:10.1136/annrheumdis-2015-208237
8. Qaseem A, McLean RM, Starkey M, Forciea MA, Clinical Guidelines Committee of the American College of Physicians. Diagnosis of Acute Gout: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med*. Published online November 1, 2016. doi:10.7326/M16-0569
9. Qaseem A, Harris RP, Forciea MA, Clinical Guidelines Committee of the American College of Physicians. Management of Acute and Recurrent Gout: A Clinical Practice Guideline From the American College of Physicians. *Ann Intern Med*. Published online November 1, 2016. doi:10.7326/M16-0570
10. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology (Oxford)*. 2007;46(8):1372-1374. doi:10.1093/rheumatology/kem056a
11. Fitzgerald J, Dalbeth N, Mikuls T, et al. 2020 American College of Rheumatology Guideline for the Management of Gout. Arthritis and Rheumatology. 2020;72:879-895.
12. Khanna D, Khanna PP, Fitzgerald JD, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res (Hoboken)*. 2012;64(10):1447-1461. doi:10.1002/acr.21773
13. Richette P, Doherty M, Pascual E, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. *Ann Rheum Dis*. Published online July 25, 2016:annrheumdis-2016-209707. doi:10.1136/annrheumdis-2016-209707
14. Adler Y, Charron P, Imazio M et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases. European Heart Journal. 2015;36:2921-2964. Accessed September 21, 2020. https://academic-oup-com.liboff.ohsu.edu/eurheartj/article/36/42/2921/2293375
15. Smith E, Yazici Y. Treatment of Behcet's Syndrome. UpToDate. August 2020. Accessed August 28, 2020.
16. Lutschinger L, Rigopoulos A, Schlattmann P, et al. Meta-analysis for the Value of Cochicine for the Therapy of Pericarditis and of Postpericardiotomy Syndrome. BMC Cardiovascular Disorders. 2019;19:207.
17. Kanbay M, Afsar B, Siriopol D, et al. Effect of Uric Acid-Lowering Agents on Cardiovascular Outcome in Patients With Heart Failure: A Systematic Review and Meta-Analysis of Clinical Studies. *Angiology*. 2020;71(4):315-323. doi:10.1177/0003319719897509
18. Borghi C, Perez-Ruiz F. Urate lowering therapies in the treatment of gout: a systematic review and meta-analysis. :12.
19. Liu C-W, Chang W-C, Lee C-C, et al. The net clinical benefits of febuxostat versus allopurinol in patients with gout or asymptomatic hyperuricemia – A systematic review and meta-analysis. *Nutrition, Metabolism and Cardiovascular Diseases*. 2019;29(10):1011-1022. doi:10.1016/j.numecd.2019.06.016
20. Zeng XX, Tang Y, Hu K, et al. Efficacy of febuxostat in hyperuricemic patients with mild-to-moderate chronic kidney disease: a meta-analysis of randomized clinical trials. *Medicine*. 2018;97(13):e0161. doi:10.1097/MD.0000000000010161
21. Singh TP, Skalina T, Nour D, et al. A meta-analysis of the efficacy of allopurinol in reducing the incidence of myocardial infarction following coronary artery bypass grafting. *BMC Cardiovasc Disord*. 2018;18. doi:10.1186/s12872-018-0881-6
22. Wu J-Y, Chang Y-T, Lin Y-C, et al. Efficacy and Safety of Lesinurad in Patients with Hyperuricemia Associated with Gout: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*. 2018;38(11):1106-1119. doi:10.1002/phar.2183
23. Gois PHF, Souza ER de M. Pharmacotherapy for hyperuricemia in hypertensive patients. Cochrane Hypertension Group, ed. *Cochrane Database of Systematic Reviews*. Published online April 13, 2017. doi:10.1002/14651858.CD008652.pub3
24. Zhang T, Pope JE. Cardiovascular effects of urate-lowering therapies in patients with chronic gout: a systematic review and meta-analysis. *Rheumatology*. 2017;56(7):1144-1153. doi:10.1093/rheumatology/kex065

25. Bredemeier M, Lopes LM, Eisenreich MA, et al. Xanthine oxidase inhibitors for prevention of cardiovascular events: a systematic review and meta-analysis of randomized controlled trials. *BMC Cardiovasc Disord*. 2018;18. doi:10.1186/s12872-018-0757-9
26. Papageorgiou N, Briasoulis A, Lazaros G, Imazio M, Tousoulis D. Colchicine for prevention and treatment of cardiac diseases: A meta-analysis. *Cardiovascular Therapeutics*. 2017;35(1):10-18. doi:10.1111/1755-5922.12226
27. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. *Ann Rheum Dis*. Published online April 6, 2018:annrheumdis-2018-213225. doi:10.1136/annrheumdis-2018-213225
28. Leccese P, Ozguler Y, Christensen R, et al. Management of skin, mucosa and joint involvement of Behçet's syndrome: A systematic review for update of the EULAR recommendations for the management of Behçet's syndrome. *Seminars in Arthritis and Rheumatism*. 2019;48(4):752-762. doi:10.1016/j.semarthrit.2018.05.008
29. Aloprim (allopurinol injectable) [product information]. Rockford, IL: Mylan Institutional LLC., August 2020.
30. Uloric (febuxostat) [product information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc., 2/2019.

Appendix 1: Current Preferred Drug List

Generic	Brand	Form	PDL
allopurinol	ALLOPURINOL	TABLET	Y
allopurinol	ZYLOPRIM	TABLET	Y
probenecid/colchicine	PROBENECID-COLCHICINE	TABLET	Y
colchicine	COLCHICINE	CAPSULE	N
colchicine	MITIGARE	CAPSULE	N
colchicine	GLOPERBA	SOLUTION	N
colchicine	COLCHICINE	TABLET	N
colchicine	COLCRYS	TABLET	N
febuxostat	FEBUXOSTAT	TABLET	N
febuxostat	ULORIC	TABLET	N
probenecid	PROBENECID	TABLET	N
allopurinol sodium	ALLOPURINOL SODIUM	VIAL	
allopurinol sodium	ALOPRIM	VIAL	
pegloticase	KRYSTEXXA	VIAL	
rasburicase	ELITEK	VIAL	

Appendix 2: Abstracts of Comparative Clinical Trials

Colchicine in Patients with Chronic Coronary Disease

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Abstract

Background: Evidence from a recent trial has shown that the antiinflammatory effects of colchicine reduce the risk of cardiovascular events in patients with recent myocardial infarction, but evidence of such a risk reduction in patients with chronic coronary disease is limited.

Methods: In a randomized, controlled, double-blind trial, we assigned patients with chronic coronary disease to receive 0.5 mg of colchicine once daily or matching placebo. The primary end point was a composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularization. The key secondary end point was a composite of cardiovascular death, spontaneous myocardial infarction, or ischemic stroke.

Results: A total of 5522 patients underwent randomization; 2762 were assigned to the colchicine group and 2760 to the placebo group. The median duration of follow-up was 28.6 months. A primary end-point event occurred in 187 patients (6.8%) in the colchicine group and in 264 patients (9.6%) in the placebo group (incidence, 2.5 vs. 3.6 events per 100 person-years; hazard ratio, 0.69; 95% confidence interval [CI], 0.57 to 0.83; P<0.001). A key secondary end-point event occurred in 115 patients (4.2%) in the colchicine group and in 157 patients (5.7%) in the placebo group (incidence, 1.5 vs. 2.1 events per 100 person-years; hazard ratio, 0.72; 95% CI, 0.57 to 0.92; P = 0.007). The incidence rates of spontaneous myocardial infarction or ischemia-driven coronary revascularization (composite end point), cardiovascular death or spontaneous myocardial infarction (composite end point), ischemia-driven coronary revascularization, and spontaneous myocardial infarction were also significantly lower with colchicine than with placebo. The incidence of death from noncardiovascular causes was higher in the colchicine group than in the placebo group (incidence, 0.7 vs. 0.5 events per 100 person-years; hazard ratio, 1.51; 95% CI, 0.99 to 2.31).

Conclusions: In a randomized trial involving patients with chronic coronary disease, the risk of cardiovascular events was significantly lower among those who received 0.5 mg of colchicine once daily than among those who received placebo. (Funded by the National Health Medical Research Council of Australia and others; LoDoCo2 Australian New Zealand Clinical Trials Registry number, ACTRN12614000093684.).

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

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BACKGROUND

Experimental and clinical evidence supports the role of inflammation in atherosclerosis and its complications. Colchicine is an orally administered, potent antiinflammatory medication that is indicated for the treatment of gout and pericarditis.

METHODS
We performed a randomized, double-blind trial involving patients recruited within 30 days after a myocardial infarction. The patients were randomly assigned to receive either low-dose colchicine (0.5 mg once daily) or placebo. The primary efficacy end point was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalization for angina leading to coronary revascularization. The components of the primary end point and safety were also assessed.
RESULTS
A total of 4745 patients were enrolled; 2366 patients were assigned to the colchicine group, and 2379 to the placebo group. Patients were followed for a median of 22.6 months. The primary end point occurred in 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group (hazard ratio, 0.77; 95% confidence interval [CI], 0.61 to 0.96; P=0.02). The hazard ratios were 0.84 (95% CI, 0.46 to 1.52) for death from cardiovascular causes, 0.83 (95% CI, 0.25 to 2.73) for resuscitated cardiac arrest, 0.91 (95% CI, 0.68 to 1.21) for myocardial infarction, 0.26 (95% CI, 0.10 to 0.70) for stroke, and 0.50 (95% CI, 0.31 to 0.81) for urgent hospitalization for angina leading to coronary revascularization. Diarrhea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group (P=0.35). Pneumonia was reported as a serious adverse event in 0.9% of the patients in the colchicine group and in 0.4% of those in the placebo group (P=0.03).
CONCLUSIONS
Among patients with a recent myocardial infarction, colchicine at a dose of 0.5 mg daily led to a significantly lower risk of ischemic cardiovascular events than placebo. (Funded by the Government of Quebec and others; COLCOT ClinicalTrials.gov number, **NCT02551094. opens in new tab**)

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to August 19, 2020

Search Strategy:

#	Searches	Results
1	Allopurinol/	7612
2	probenacid.mp.	2
3	colchicine.mp. or Colchicine/	20438
4	febuxostat.mp. or Febuxostat/	946
5	pegloticase.mp.	158
6	rasburicase.mp.	428
7	1 or 2 or 3 or 4 or 5 or 6	28781
8	limit 7 to (english language and humans and yr="2016 -Current")	1896
9	limit 8 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	91

Appendix 4: Key Inclusion Criteria

Population	Patients with acute and chronic gout, recent MI, pericarditis or Behçet's Syndrome
Intervention	Gout drugs
Comparator	Active comparators or placebo
Outcomes	Pain reduction, prevention of recurrent inflammatory condition, prevention of recurrent pericarditis, prevention of CV events, and/or CV death
Timing	At symptom onset
Setting	Outpatient

Appendix 5: Prior Authorization Criteria

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
- Long-term colchicine use (>10 tablets every 180 days)

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 #7
4. Does the patient have a diagnosis of Behcet's Syndrome with mucocutaneous and/or joint involvement (concomitant NSAID is appropriate)?	**Yes:** Approve for up to 12 months	**No:** Go to #5
5. Does the patient have a cardiovascular diagnosis for which colchicine has demonstrated benefit (e.g., pericarditis, recent myocardial infarction or high cardiovascular disease risk [concomitant NSAID is appropriate])?	**Yes:** Approve for up to 12 months	**No:** Go to #6
6. Does the patient have gout and failed NSAID therapy or have contraindications to NSAIDs or is a candidate for combination therapy, due to failure of monotherapy or initial presentation justifies combination therapy (i.e., multiple joint involvement and severe pain)?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; recommend trial of NSAID
7. Is the request for febuxostat?	**Yes:** Go to #8	**No:** Go to #9

Approval Criteria		
8. Has the patient tried and failed allopurinol or has contraindications to allopurinol?	**Yes:** Approve for up12 months	**No:** Pass to RPh. Deny; recommend trial of allopurinol
9. Is the request for probenecid?	**Yes:** Go to # 10	**No:** Pass to RPh. Deny; medical appropriateness
10. Has the patient tried allopurinol and febuxostat or have contraindications to one or both of these treatments?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; recommend a trial of allopurinol or febuxostat

P&T/DUR Review: *12/20 (KS), 1/17 (KS)*
Implementation: *1/1/2021; 4/1/2017*