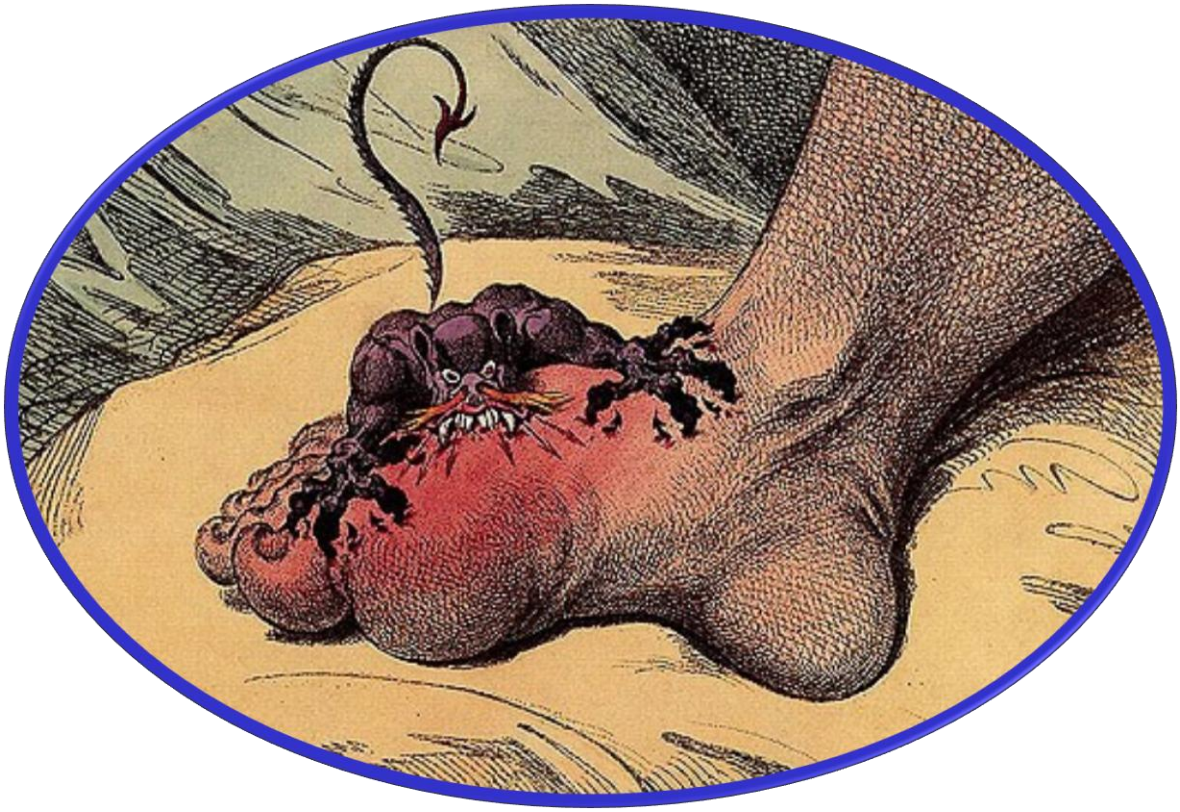
Gout….



Update 2013

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"Seek simplicity, and mistrust it."
Alfred North Whitehead

Table of Contents

Tables and Appendices

Definitions and Abbreviations

ACR	American College of Rheumatology
AE	Adverse event
AHS	Allopurinol hypersensitivity syndrome
CrCl	Creatinine clearance
eGFR	Estimated glomerular filtration rate
MI	Myocardial infarction
NICE	National Institute for Health and Care Excellence
SUA	Serum uric acid
ULT	Urate lowering therapy

Introduction

- This handout addresses issues regarding some current recommendations for the management of gout and a review of the supporting evidence.
- Gout is a condition that presents as a spectrum of clinical and pathologic features caused by an excess body burden of uric acid, manifested in part by hyperuricemia which is generally defined as a serum urate level greater than 400µmol/L.
- Tissue deposition of monosodium urate monohydrate crystals in supersaturated extracellular fluids of the joint, and certain other sites, causes most of the clinical and pathologic features of gout.
- In developing this topic we have reviewed
    - American, British, and European guidelines
    - Cochrane reviews
    - Up To Date
    - FDA reports
    - Original publications
- **We will address four questions**
    1. What are the treatment options for acute gout?
    2. How should urate lowering treatment (ULT) be started and monitored?
    3. What are some special considerations in treating gout?
    4. What is the role of lifestyle in prevention of gout?
- Treatment recommendations are frequently supported by consensus or small studies rather than large high quality randomized controlled trials. For some recommendations that may have changed recently we have provided supporting evidence in Appendix 1.
- People can have hyperuricemia without gout; asymptomatic hyperuricemia does not require treatment.
- Several drugs and conditions are associated with hyperuricemia and gout (Table 1).

Table 1 Drugs and conditions associated with hyperuricemia and gout[1]

Drugs	Conditions
Alcohol	Excessive alcohol use
Cyclosporine	Atherosclerosis
Cytotoxic chemotherapy	Chronic kidney, glomerular, interstitial renal disease
Diuretics (thiazide and loop)	Diabetes
Ethambutol	Hyperlipidemia
Interferon + ribavarin	Hypertension
Levodopa	Ischemic heart disease
Nicotinic acid (niacin)	Lead intoxication
Pyrazinamide	Metabolic syndrome
Salicylates, low-dose	Myeloproliferative disorders and some cancers
Tacrolimus	Obesity, dietary factors
Teriparatide	Urolithiasis history
	Genetic or acquired causes of uric acid overproduction (rare)

Question 1. What are the treatment options for acute gout?

- Treatment should begin as soon as possible after an acute episode starts, ideally within 24 hours.[2]
- Non-pharmacological therapy includes topical ice packs.[2]
- Various guidelines recommend the following drugs for treatment of acute episodes:
  - Colchicine
    - Used to be given until onset of GI symptoms but fixed low dose (total 1.8 mg on the first day) is now recommended because it is as effective and less likely to cause adverse effects.[3]
    - Must be given within 36 hours of onset of attack.
  - NSAIDS
    - Although indomethacin has been commonly used, there is no evidence that one NSAID is more effective than another.[4]
    - Choice of agent may depend on side effect profile.
      - Indomethacin may be more likely to cause CNS adverse effects.[5]
      - Naproxen is suggested as having the lowest cardiovascular risk (see special considerations, ischemic heart disease (page 12).[6]
    - Nonselective NSAIDs are less expensive, are readily available, and are as effective and at least as safe as selective agents.[4]
  - Oral corticosteroids
    - Useful if patient cannot take colchicine or NSAID or if the attack would not resolve otherwise.
    - Generally there is no need to taper unless patient has a history of frequent flares.[4]

- Intra-articular corticosteroids
  - Useful for patients who cannot take oral medication and who have one or two acutely inflamed joints.
  - Requires technical skill and not all physicians may be comfortable carrying out the procedure.
  - Important to **exclude infection** by joint aspiration and analysis even in patients with a history of several gout attacks.
  - Suggestion is triamcinolone acetonide[4]
    - Small joint (finger, toe) 10 mg
    - Medium joint (wrist, ankle, elbow) 30 mg
    - Large joint (knee) 40 mg

- Some guidelines express a preference for one therapy over another; other guidelines indicate all are appropriate. Choice of drug may depend on age and comorbidities such as
  - Renal function
  - Cardiovascular disease including heart failure
  - Gastroesophageal disease
  - Concurrent medications
  - Drug allergy

See Question 3, Special Considerations page 12 for further details.

- Treatment choice may depend on whether the patient is already on prophylactic colchicine. If so, and the patient has received acute colchicine therapy in the last 14 days, choose an NSAID or oral corticosteroid.[2]
- Treatment should continue **until symptoms resolve**, approximately 7 days. Generally acute gout attacks resolve spontaneously although resolution is faster with treatment.
- A summary of treatment options is in Table 2.

Question 2. How should urate lowering therapy (ULT) be started and monitored?

Starting therapy

- Guidelines[7–9] recommend initiating ULT in patients with gout and any one of:
  - 2 or more attacks of acute gouty arthritis in one year
  - Tophus or tophi by clinical exam or imaging study
  - Chronic kidney disease stage 2 or greater
  - Past urolithiasis
  - Need to continue therapy with diuretics
- Different guidelines offer various options for the initiation of ULT.
  - The American Guidelines suggest that therapy can be initiated **during an acute attack** of gout **provided that** effective anti-inflammatory or colchicine treatment has been started.[7]

- This recommendation is based on the results of a recently published single site RCT that evaluated starting allopurinol during an acute attack versus starting on day 11 after the attack started. Results reported
  - No difference in pain scores on any of days 1 to 10
  - No difference in the number of gout flares during days 1 to 30
  - All flares were at least 5 days removed from the initiation of allopurinol and none involved exacerbation of the index joint.[10]
- Other guidelines[8] suggest waiting 1-2 weeks after resolution of the acute attack as therapy may precipitate further attacks.
- Our **content expert** supports initiating allopurinol during the acute attack to achieve better compliance and long-term outcomes. Therapy should start with a low dose (50 to 100 mg daily).

- Therapy should be life-long and should not be stopped during an acute attack.

Monitoring therapy

- The therapeutic goal of ULT is to prevent acute flares, prevent the development of tophi, help dissolve existing tophi, and prevent the development of chronic gouty arthropathy.[9]
- During an acute attack, serum urate levels may **fall**. NICE suggests measuring urate 4 to 6 weeks after an acute attack of gout to confirm hyperuricemia.[8]
- Guidelines recommend that therapy should be titrated to maintain an SUA level of < 360 µmol/L, well below the saturation point for monosodium urate of 405 µmol/L.
  - The benefits associated with reaching a target SUA of < 360 µmol/L have been confirmed by retrospective observational analyses.[11–14]
  - A post hoc analysis of an RCT[15] comparing febuxostat to allopurinol reported flare rates in patients with SUA levels < 360 vs ≥ 360 µmol/L.
    - During the initial weeks of the trial, flare rates were comparable between the two groups.
    - By the last 4 weeks of the 52 week trial, the mean rate of flares among patients with a mean post baseline SUA < 360 µmol/L was significantly lower than that among patients with a mean post-baseline SUA ≥ 360 µmol/L .
      - 6% vs 14% respectively; P <0.05
      - Patients in the trial received prophylaxis for the initial 8 weeks only.
  - Although 360 µmol/L was used as the target point in most studies, another study suggests that benefit may be seen at SUA levels of < 400 µmol/L.[13] In some patients, a target of < 300 µmol/L is required to improve signs and symptoms (e.g., patients with tophaceous gout).[7]
- Monitoring serum urate levels: two approaches have been suggested:
  - <u>OPTION 1</u>: During dose titration of urate lowering therapy, check serum urate levels regularly (every 2-5 weeks). Once the target has been reached, check urate levels every 6 months.[7]

- OPTION 2: Determine the level within 2 to 4 weeks of a dose adjustment, with confirmation 3 months later. Once goal values are confirmed, measure levels every 6 months for the next year and then annually unless medications or lifestyle factors that might alter urate levels have been introduced in the interim.[16]

- Rate of lowering:
  - It is suggested to lower the serum uric acid slowly (no more than 60 to 120 µmol/L per month) to minimize the occurrence of gout flares. These occur more frequently in the early months of urate lowering treatment and might influence compliance.[16]

Pharmacologic Choices

Xanthine oxidase inhibitors (allopurinol and febuxostat)

- Allopurinol and febuxostat both inhibit production of uric acid.
- Most guidelines recommend allopurinol as first-line therapy.
- They have different chemical structures and febuxostat may be an option for patients who have a hypersensitivity to or are otherwise intolerant of allopurinol.
- According to the guidelines from ACR which do not consider **cost**, both are considered first-line options.[7]
- Allopurinol and febuxostat should **not** be used in combination.
- A recent Cochrane Review reported that after 3 years, there were no statistically significant differences regarding effectiveness and harms between febuxostat 80 mg or 120 mg and allopurinol groups.[17]
- The urate lowering efficacy of febuxostat compared to allopurinol has been studied in 3 RCTs.[15,18,19]
  - All 3 reported febuxostat, in doses of 80 mg or above, to be more effective than **fixed-dose** allopurinol (300 mg) in achieving a serum urate concentration of less than 360 µmol/L.
  - In the 2 studies that reported number of gout **flares**, there was **no difference** between febuxostat and allopurinol.
  - Authors comment that allopurinol might have been more effective at lowering urate levels if the dose had been titrated upwards as is recommended.
  - None of the RCTs included patients with CrCl <30 ml/min and none reported the mean SUA achieved in the febuxostat and allopurinol groups.

- **How to prescribe allopurinol**

Starting dose

- Usual starting dose is 100 mg once a day (preferably taken with food).
- Guidelines suggest starting at 50 mg/day in patients with
  - Stage 4 or 5 chronic kidney disease;[7] NICE suggests Stage 3[8]
  - Frequent attacks
  - Hepatic impairment, and
  - In the elderly.[8]
- An alternative approach for patients with **renal insufficiency** to minimize the risk of allopurinol hypersensitivity syndrome is a starting dose of 1.5 mg per ml/min of eGFR.[20] A suggested regimen[20] for **starting** allopurinol at different levels of eGFR is

Stage of Kidney Function	eGFR	Starting dose
Stage 5	<5	50 mg/week
Stage 5	5-14	50 mg twice weekly
Stage 4	15-29	50 mg every 2 days
Stage 3B	30-44	50 mg/day
Stage 3A	45-59	50 mg/100 mg on alternate days
Stage 2	60-89	100 mg/day
Stage 1 (normal)	90-130	150 mg/day
Stage 1 (normal)	>130	200 mg/day

  - Dose increments should be no more than 50 mg daily every 4 weeks to the minimum daily dose necessary to achieve the SUA target level.[16]

Titrating to target and maximum dose

- Gradually increase dose every 2-4 weeks by 100 mg (50 mg if initial dose is 50 mg) to achieve SUA target.
- Dose range is 100 mg to 800 mg daily; commonly 300 mg daily.[5]
  - Doses over 300 mg should be taken in **divided doses** to help minimize any gastrointestinal adverse effects. [8]
- Dose can be raised above 300 mg daily, even in patients with renal impairment, provided that it is accompanied be adequate patient education and monitoring for drug toxicity (e.g. pruritus, rash, elevated hepatic transaminases).[7]

Allopurinol Hypersensitivity Syndrome (AHS)

- This life-threatening toxicity syndrome is characterized by vasculitis, rash, eosinophilia, hepatitis, and progressive renal failure.[21]
- Onset of symptoms frequently occurs after 2 to 8 weeks of starting allopurinol.[22]
- Mortality rates of 15% to 37.5% have been reported.[21]
- The syndrome probably involves an interaction of metabolite accumulation and a drug specific immune response.[24]
- Predisposing factors include: advanced age, Southeast Asian/Chinese ethnicity, renal impairment, and high allopurinol initiation dosages.[25]
- Our content expert stressed the importance of informing patients to report if they experience **any NEW pruritus or skin rash** as this represents allopurinol intolerance and might be an initial indicator of **allopurinol hypersensitivity syndrome**.
- Following current recommendations, especially starting with low dose and increasing slowly, the risk of AHS is lower than previously thought.
- A recently published retrospective case-control study concluded that starting allopurinol at a dose of 1.5 mg per unit of eGFR may be associated with a reduced risk of AHS. [20]
- Before starting allopurinol, consider HLA-B*5801 in **selected patients**, specifically in subpopulations at higher risk for severe allopurinol hypersensitivity reactions (e.g. Koreans with stage 3 or worse CKD, and Han Chinese and Thai irrespective of renal function).[7] If the test is positive in these subpopulations, do not prescribe allopurinol.

- **Febuxostat**
  - In Canada, febuxostat is available only as an 80 mg tablet and this is the usual recommended dose.
  - According to the official monograph[26] no dosage adjustment is needed in
    - Elderly patients
    - Patients with mild to moderate hepatic impairment (Child-Pugh Class A or B)
    - Patients with mild or moderate renal impairment (CrCl 30-89 ml/min)

Uricosuric agents

- Probenecid is the commonly referred to uricosuric agent for urate lowering.
  - Tablets are no longer being manufactured for the Canadian market but capsules may be available from some compounding pharmacies.
- Uricosuric agents are **not recommended** in patients with
  - eGFR below 50 ml/min
  - A history of urolithiasis
- Patients should increase fluid intake.[27]

Uricases

- Pegloticase, a recombinant pegylated uricase, is an expensive biologic therapy approach for gout.
  - It is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULT options.[7]
- It is currently not available in Canada.

Prophylaxis while starting ULT

- Initiation of any urate lowering therapy may precipitate acute gouty flares because of the sudden decrease in SUA levels.[2]
- To minimize the risk of flares, prophylactic therapy is recommended.[16]
- Low doses of colchicine or NSAIDs may be used for prophylactic therapy.(See Table 2)
  - For patients who cannot tolerate either of these therapies, low dose oral prednisone (≤ 10 mg daily) may be used.[2] This is a consensus recommendation with little evidence of the benefit of this low dose and the known risks of prolonged corticosteroid use.
- <u>Duration of prophylactic therapy during the initiation of ULT</u>:
  - The ACR guidelines [2] recommend continuing prophylaxis if there is any clinical evidence of continuing gout disease activity and/or the target SUA has not yet been achieved.
    - Continue prophylaxis for the greater of:
      - 6 months' duration[15, 19, 28]
      - 3 months after achieving the target SUA level appropriate for the patient without tophi detected on physical examination
      - 6 months after achieving the target SUA level appropriate for the patient where there has been resolution of tophi previously detected on physical examination.
  - Because of potential toxicity, the continued use of colchicine or NSAIDs beyond these recommended durations is not recommended.[16]
  - **Our content expert suggests:**
    - Colchicine is the drug of first choice for prophylaxis.
      - A dose of 0.6 mg daily is effective for most patients.
      - Dose range is usually 0.6 to 1.2 mg daily and 1.8 mg is the high maximum. Regimens greater than 0.6 mg daily should be given in divided doses.
      - Patients with very high SUA levels may be started on 1.2 mg daily and can be decreased to 0.6 mg daily if no attacks occur after a few months, or if diarrhea occurs.
    - Duration of prophylaxis:
      - At least 3 months after last attack, provided normouricemia is attained.

Question 3. What are some special considerations when treating gout?

- Elderly patients may have comorbidities or be taking other medications that limit the use of NSAIDS or colchicine; oral corticosteroids may be appropriate.[4]
- End stage renal disease and renal transplantation: Colchicine is not removed by dialysis and NSAIDs may further decrease renal function and may be associated with a high risk of upper GI bleeding in dialysis patients. Oral corticosteroids may be appropriate.[4]
- Renal impairment and NSAIDS
  - The following is the recommendation from our local nephrologist
    - Caution against the use of **any NSAID** in all patients with chronic kidney disease
      - eGFR <60 ml/min, or
      - a higher GFR (stage I and II CKD) with significant proteinuria
    - These drugs all accumulate in patients with advanced CKD stages 4 and 5 (eGFR<30) and one would thus expect greater risk of adverse effects including GI bleeding.
    - NSAIDS cause reduced renal blood flow, acute functional renal failure, hyporeninemic hypoaldosteronism with hyperkalemia, edema and hypertension as well as hematuria, papillary necrosis, nephrotic syndrome with minimal change disease, proliferative glomerulonephritis, acute interstitial nephritis, and acute tubular necrosis. Whether NSAIDs can cause chronic interstitial nephritis is unclear although this remains likely. As well, NSAIDs will antagonize all antihypertensive drugs and make hypertension worse.
    - For patients with acute gout and CKD, colchicine rather than any NSAID is recommended. Prednisone would be the next drug to use after colchicine. If a NSAID has to be used then sulindac **may** have a lower renal risk as it does not decrease urinary prostaglandin levels to the same extent as other NSAIDs.
- History of ischemic heart disease or heart failure:
  - Short term or long term use of NSAIDs can exacerbate heart failure.
  - Long term use of NSAIDs has been associated with increased risk of MI. Naproxen appears to be least likely to show this association.[6]
  - A large nationwide cohort study found that even **short-term** use of most NSAIDs was associated with increased risk of death and recurrent MI in patients **with prior MI**.
    - When analyzed by the individual NSAID, only diclofenac was associated with an increased risk when taken for periods of 7 days of less (hazard ratio, 3.26; 95% confidence interval, 2.57 to 3.86 for death/MI at day 1 to 7 of treatment).
    - Use of naproxen was not associated with a significantly increased risk of death or MI for treatments up to 90 days in duration, but point estimates suggested increased risk and confidence intervals were large.
    - The study concluded that neither short- nor long-term treatment with NSAIDs is advisable in a population with a history of prior MI.[29]
- Concomitant anticoagulation: Avoid NSAIDs in patients on anticoagulation and prescribe low-dose colchicine or oral corticosteroids.[4]

- Concomitant diuretics: Diuretics increase urate levels by decreasing urate excretion in a **dose-dependent** relationship.[30] Use of thiazides and loop diuretics is significantly associated with the development of gout; this association has not been shown for potassium-sparing agents such as triamterene and spironolactone.[31]
  - Asymptomatic diuretic-induced hyperuricemia is not an indication for discontinuing the diuretic or adding urate lowering therapy.
  - For diuretic-induced gout, the approach may vary according to the indication for the diuretic:
    - Edema and HF: It may not be advisable to stop the diuretic and higher doses of allopurinol may be needed to achieve urate target levels.[32]
    - Hypertension: ACE inhibitors and angiotensin receptor blockers (ARBs) may attenuate the rise in urate from diuretics and augment their antihypertensive effect so a lower dose of diuretic may be required for control of hypertension. Losartan, in particular appears to have uricosuric activity.[33-35] Replacing the diuretic-induced fluid loss will also mitigate the rise in urate.
  - Most patients with diuretic-induced gout are treated with ULT such as allopurinol.[32]
    - Our content expert suggests substituting the diuretic with losartan, if that is an option in a particular situation.

Question 4. What is the role of lifestyle in prevention of gout?

- Recommendations for advising patients about lifestyle have changed somewhat.
- Gout is associated with cardiovascular disease, hypertension, abdominal obesity, hyperlipidemia, and diabetes. Lifestyle recommendations for prevention of gout should not contradict recommendations that would benefit those associated conditions.
- Evidence for the benefit of lifestyle changes comes from observational studies rather than randomized controlled trials.[7] Therefore the findings represent associations of lifestyle factors with gout and not necessarily a causal link between those factors and gout.
- Whereas previously there were recommendations to limit intake of high purine fruit and vegetables, this is no longer the case since intake of fruits and vegetables will benefit the other conditions associated with gout.
- The US Guideline[7] makes general recommendations and specific recommendations to avoid, limit, or encourage intake of various foods.
    - General recommendations include:
        - Weight loss for obese patients, to achieve normal BMI
        - Exercise
        - Smoking cessation
        - Healthy overall diet
        - Stay well hydrated
    - Specific dietary recommendations include
        - **Avoiding** organ meats high in purine content and high fructose corn syrup sweetened beverages or foods
        - **Limiting** red meats, seafood with high purine content (e.g., sardines, shellfish), naturally sweet fruit juices, sweetened food products and sodium rich foods
        - Alcohol overuse should be **avoided** (defined as more than 2 servings a day for men and 1 serving a day for women). This applies specifically to beer and spirits, but amounts of wine should also be limited.
        - Low or non-fat dairy products are **encouraged**.
- In addition, drinking at least 3 to 4 or more cups of coffee (including decaffeinated) has been associated with a decreased incidence of gout.[36]
- While adherence to lifestyle recommendations will help prevent gout flares, most patients will require drug therapy for optimal results.[7]

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Table 2 Summary of oral drug treatments for acute and prophylactic treatment of gout

Drug/*Class*	Dose	Adverse Effects	Renal/hepatic considerations	Comment	Cost for 7 & 30 days[a]
Colchicine	ACUTE 1.2 mg stat then 0.6 mg 1 hour later for total 1.8 mg on the first day 0.6 mg once or twice daily PROPHYLAXIS FOR ULT 0.6 mg once or twice daily for 6 to 12 months	Abdominal pain and cramps, diarrhea, nausea, vomiting	For acute flare: If CrCl <30 ml/min do not repeat treatment course more often than once every two weeks.[37] For patients on dialysis total recommended dose for acute flare is 0.6 mg.[37] No dose adjustment necessary for hepatic impairment but with severe impairment do not repeat treatment course more than once every 2 wks[37] For prophylaxis: CrCl <30 mL/min: start at 0.3mg daily & monitor closely if dose increases are required. Patients on dialysis, 0.3 mg twice weekly; monitor closely Consider dosage reduction in severe hepatic impairment.[38]	Not recommended for acute treatment if cannot be given < 36 hours after onset[2] Concomitant use with P-gp and cytochrome P450 inhibitors can lead to colchicine toxicity (e.g., erythromycin, clarithromycin, verapamil, azole antifungals, anti-virals, cyclosporine Lipid-lowering agents (statins and fibrates) increase the risk of rhabdomyolysis) CHECK WITH PHARMACIST or DRUG INTERACTION REFERENCE FOR PATIENT-SPECIFIC INTERACTIONS	$ 3.85/ 7 days $ 7.70 – 15.40/ 30 days
Naproxen *NSAID*	ACUTE 750 mg stat then 500 mg BID PROPHYLAXIS FOR ULT 250 MG BID	GI upset, fluid retention, hypertension, renal impairment.	Contraindicated with - CrCl <30 ml/min[1,38] - CVD especially heart failure and hard to control hypertension - Coagulopathy or anticoagulant therapy Caution advised if CrCL < 60mL/min)	May need gastroprotection depending on risk. Contraindicated with active gastroduodenal ulcer All NSAIDs carry black box warnings concerning serious cardiovascular thrombotic events which can be fatal, and risk of serious gastrointestinal adverse events especially in the elderly. Naproxen appears to have lowest CV risk of any NSAID. No evidence that indomethacin is more	$2.95/ 7 days (500 mg bid) $6.41/ 30 days (250 mg bid)
Indomethacin *NSAID*	ACUTE 50 mg TID	GI upset, fluid retention, hypertension, renal	Caution advised[38] if CrCl < 60mL/min) Liver disease: Child-Pugh Class III,		$ 9.37/ 7 days (50 mg tid)

	PROPHYLAXIS FOR ULT No mention of use of indomethacin for prophylaxis in any reference consulted, although not specifically contraindicated for this	impairment. Neurological: Headache, dizziness, somnolence [38]	initiate with lowest recommended dosage, monitor patient closely and reduce dosage if necessary Elderly: initiate with the lowest recommended dosage, monitor patient closely	effective than other NSAIDs. Indomethacin more likely to cause neurological adverse effects ~10%	
Prednisone *Corticosteroid*	ACUTE 0.5 mg/kg/day for 5 to 7 days [2] PROPHYLAXIS FOR ULT ≤ 5 – 10 mg/day Usually reserved for people with end-stage renal disease or those who cannot take NSAIDs or colchicine	Hypertension, edema, impaired glucose tolerance, increased appetite, osteoporosis, disturbance in mood [38]	Renal insufficiency: no adjustment necessary Not removed by hemodialysis [38] No information on dosing in hepatic insufficiency, except a precaution that corticosteroid effect may be increased in cirrhosis, due to decreased metabolism. [38]	Does not need to be tapered when given for acute treatment. Prophylactic use is not well supported by evidence and is almost certain to cause adverse effects.	$1.96/ 7 days (70 Kg patient, 35 mg/day)
Urate Lowering Therapy					
Allopurinol *Xanthine oxidase inhibitor*	Start 50 or 100 mg/day Increase by 50 or 100 mg/day q 2 – 4 weeks to maximum of 800 mg	Skin rash, GI upset, hepatotoxicity, fever, hypersensitivity syndrome, xanthine stones	Start 1.5 mg/mL/min eGFR Increase by 50 mg q 2-4 weeks [16, 20]	Starting dose of 50 mg/day is recommended in the elderly and patients with hepatic impairment or frequent attacks.[8]	$ 6.38/ 30 days (300 mg/d) $15.60/ 30 days (800 mg/d)
Febuxostat *Xanthine oxidase inhibitor*	80 mg daily	Nausea, arthralgia, skin rash (at higher dose), increased hepatic aminotransferase levels.	Mild to moderate renal impairment: (CrCl, 30-89 mL/min), no dosage adjustment necessary. Mild to moderate hepatic impairment: (Child-Pugh class A or B), no dosage adjustment necessary. [38]	NS Pharmacare covers febuxostat only in patients who have documented hypersensitivity to allopurinol	$ 51.76/ 30 days (80 mg/day)

a wholesale costs from McKesson Pharmaclik online as of Nov 15, 2013 and do not include prescribing fee

Appendix 1 Table of select gout studies

Author Year	N Length	Population	Comparators	Outcome	Results	Comments/Implications
High vs low dose colchicine for acute treatment of gout						
Terkeltaub [3] 2010	185 32 hrs	At least 2 gout flares previous 12 mos 95% male Mean age 51	High dose: colchicine 1.2 mg followed by 0.6 mg hourly for 6 hrs (4.8 mg total) Low dose colchicine 1.2 mg followed by 0.6 mg (1.8 mg total) Placebo	≥ 50 reduction in pain intensity Serious adverse events	Pain relief No sig diff b/w high and low dose colchicine in pain relief. NNT for both doses vs placebo = 5 Adverse events High dose: 77% had AE all of which included diarrhea. 19 % had serious AE. Low dose: 37% had AE 23% of which had diarrhea. None had serious AE. NNH for high dose vs low dose or placebo ~ 2.	Colchicine had to be given within 12 hours which may not always be possible. Industry funded trial with one author holding 2 patents pertaining to dosing of colchicine with clarithromycin. Low dose colchicine is as effective as high dose colchicine with far fewer AEs.
Starting allopurinol during an acute gout flare						
Taylor [10] 2012	57 30 days	Presenting within 7 days of acute gout attack 100% male Mean age ~60	Allopurinol 300mg daily Placebo Both given for 10 days starting within 7 days of onset of acute attack All patients given allopurinol 300 mg daily on days 11-30	Pain score on day 1 to 10 Gout flares day 1 to 30	Pain score No sig diff. Went from ~6.5/10 to ~0.23 at day 10 Duration of incident attack No sig diff. ~ 4 days in each group Gout flares day 1 to 30 2 in allopurinol group 3 in placebo group	Limitation is that this is a small, single-centred study with all male subjects. All patients received indomethacin 50 mg TID for 10 days and colchicine 0.6 mg BID for 90 days. In uncomplicated gout NSAID, prophylactic colchicine 0.6 mg BID, and allopurinol may be started during an acute attack.

Author Year	N Length	Population	Comparators	Outcome	Results	Comments/Implications
Allopurinol vs Febuxostat						
Schumacher[18] 2008	1072 28 weeks	Diagnosis of gout Serum urate >480 94% male Mean age 52 Creatinine <177 Creatinine >133 = 4%	Febuxostat 80 mg Febuxostat 120 mg Febuxostat 240 mg Allopurinol 100 mg if creatinine >133 or 300 mg if creatinine <133 Placebo	Proportion of subjects with urate <360 Adverse events	<u>Proportion of subjects with urate <360 at 28 weeks:</u> - Febuxostat 80 mg 76% - Febuxostat 120 mg 87% - Febuxostat 240 mg 94% - Allopurinol 41% - Placebo 1%	8 weeks of prophylaxis provided with naproxen 250 mg BID or colchicine 0.6 mg QD Not enough subjects with renal impairment to be able to definitively determine efficacy or harms. Febuxostat 240 was included for safety rather than efficacy analysis. Generally there was no clinically significant difference in AEs among the groups, although febuxostat 240 mg had higher rates of joint-related symptoms (13% vs 7%), diarrhea (13% vs 6%) and dizziness (7% vs 2%) than allopurinol. Mean levels of urate acid achieved in each group were not reported. Febuxostat led to more subjects achieving target urate level but allopurinol was given at fixed doses and not titrated.
Becker [15] 2005	762 52 weeks	Diagnosis of gout Serum urate >480 96% male Mean age 52 Mean urate ~585 Creatinine <133 or CrCl > 50 ml/min	Febuxostat 80 mg Febuxostat 120 mg Allopurinol 300 mg	Proportion of subjects with urate <360 Acute flares Adverse events	<u>Proportion of subjects with urate <360 at last 3 monthly visits:</u> - Febuxostat 80 mg 53% - Febuxostat 120 mg 62% - Allopurinol 300 mg 21% <u>Gout flares</u> - Febuxostat 80 mg 22% - Febuxostat 120 mg 36% - Allopurinol 300 mg 21%	More patients achieved urate target level but there was no difference in number of flares between febuxostat 80 mg and allopurinol 300 mg. Allopurinol was given at fixed dose and not titrated as you would expect over a one year period.

Author Year	N Length	Population	Comparators	Outcome	Results	Comments/Implications
					Adverse events No difference between groups	
Becker [19] 2010	2269 6 months	Diagnosis of gout Serum urate >480 94% male Mean age 53 Mean urate ~576 CrCl 30-59 ml/min = 18%	Febuxostat 40 mg Febuxostat 80 mg Allopurinol 200 mg if CrCl < 60 ml/min or 300 mg if CrCl ≥ 60 ml/min	Proportion of subjects with urate <360 Adverse events	Proportion of subjects with urate <360 at last visit: - Febuxostat 40 mg 45% - Febuxostat 80 mg 67% - Allopurinol 2-300mg 42% Results were similar in patients with renal impairment Adverse events No difference between groups	Febuxostat 40 mg was non-inferior to allopurinol in all outcomes. Febuxostat 80 mg was more effective in lowering urate to target levels than allopurinol but not more effective in reducing flares.
Low starting dose to decrease risk of allopurinol hypersensitivity syndrome (AHS)						
Stamp [20] 2012	211	Gout cases with and without AHS	Doses of allopurinol in relation to eGFR	Development of AHS	90% of AHS cases occurred within first 180 days Mean starting dose of allopurinol for - controls = 112 mg/d - cases = 184 mg/d Increase in AHS as starting dose of allopurinol increased	Case-control study, not RCT. Analysis indicated a reasonable practical starting dose of allopurinol to minimize risks of AHS is 1.5 mg/ml/min eGFR.