Pharmacotherapy 2

Gout

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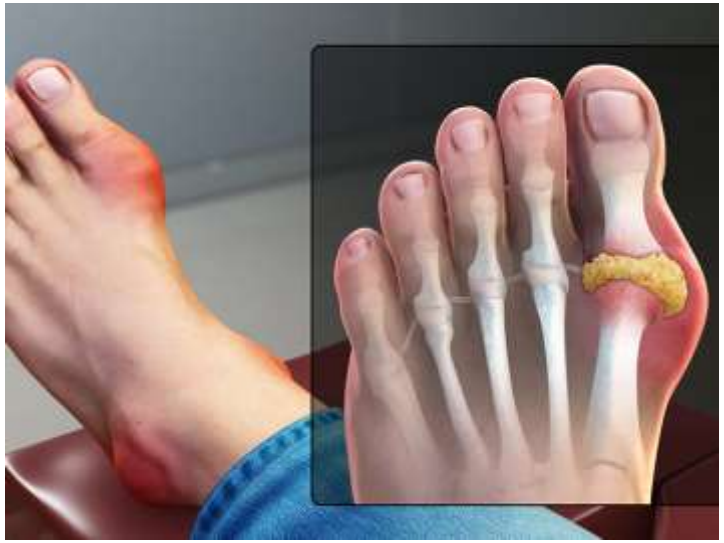
Gout

General Principles

- ✓ Hippocrates described it as arthritis of the rich' due to the association with certain foods & alcohol.
- ✓ Gout is caused by deposition of monosodium urate crystals in joints and soft tissues following chronic hyperuricaemia.
- ✓ Chronic hyperuricaemia is associated with disorders of purine metabolism due to under excretion or over production of uric acid.
- ✓ Gout usually presents as a monoarthritis in the first metatarsophalangeal joint (big toe) of the foot and is often referred to as podagra (from the Greek 'seizing the foot').



- ✓ Monosodium urate crystals preferentially form in cartilage and fibrous tissues where they are protected from contact with inflammatory mediators.
- ✓ The deposition of crystals may continue for months or years without causing symptoms; it is only when the crystals are shed into the joint space that inflammatory reaction occurs precipitating an acute attack of gout.
- ✓ The shedding of crystals can be triggered by a number of factors including direct trauma, dehydration, acidosis or rapid weight loss.
- ✓ The most appropriate time to measure serum urate for monitoring purposes is when the attack has completely resolved.
- ✓ Although the attack is extremely painful, it is usually self-limiting resolving spontaneously in 1–2 weeks.
- ✓ Inappropriate management of gout can result in chronic tophaceous gout with polyarticular, destructive low-grade joint inflammation, joint deformity and tophi.

✓ Risk factors:

- Hyperuricaemia is one of the main risk factors - occurs in about 15–20% of the population
- Genetics: Common primary gout in men often shows a strong familial predisposition (the genetic basis for this is not fully understood).
- Renal disease: Gout is frequently associated with kidney disease, each being a risk factor for the other.
- Co-morbidities
- Studies have shown obesity, weight gain and hypertension all to be independent risk factors for the development of gout.

Box 54.1 Risk factors for gout

Genetics
Renal disease
Co-morbidities, for example, obesity, dyslipidaemia, glucose intolerance, hypertension
Diet
Alcohol consumption
Medication

- Diet: Gout has often been associated with a rich lifestyle and excesses in diet (red meat, seafood, but not a diet high in purine-rich vegetables).

- Alcohol: Increased daily consumption of alcohol is associated with a higher risk of gout. Alcohol also raises lactic acid levels in blood, which inhibits uric acid excretion.

- Medication: A number of drugs are associated with increased uric acid levels - Table 109-2.

- Radiotherapy and chemotherapy in patients with neoplastic disorders can cause hyperuricaemia because of increased cell breakdown.

Table 54.1 Causes of primary and secondary gout

Primary gout	Secondary gout
Idiopathic	Increased uric acid production
Rare enzyme deficiencies	Lymphoproliferative/ Myeloproliferative
Hypoxanthine-guanine phosphoribosyl transferase deficiency (HPRT)	Chronic haemolytic anaemias
Phosphoribosyl pyrophosphate synthetase super-activity	Secondary polycythemia
Ribose-5-phosphate	Severe exfoliative psoriasis
AMP-deaminase deficiency	Gaucher's disease
	Cytotoxic drugs
	Glucose-6 phosphate deficiency
	High purine diet
	overproduction
	Reduced uric acid secretion
	Renal failure
	Hypertension
	Drugs (diuretics, aspirin, ciclosporin)
	Lead nephropathy
	Alcohol
	Down's Syndrome
	Myxoedema
	Beryllium poisoning

TABLE 109-2 Drugs Capable of Inducing Hyperuricemia and Gout

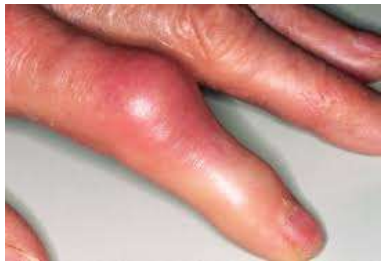
Diuretics	Ethanol	Ethambutol
Nicotinic acid	Pyrazinamide	Cytotoxic drugs
Salicylates (<2 g/day)	Levodopa	Cyclosporine

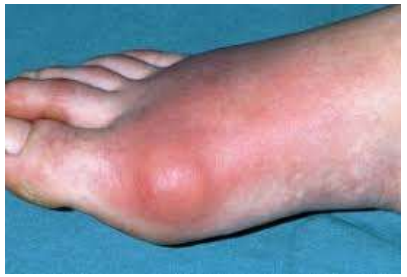
TABLE 109-3 Clinical Manifestations of Gout

Classic acute gout ("podagra")	Monoarticular arthritis Frequently attacks the first metatarsophalangeal joint, although other joints of the lower extremities are also frequently involved Affected joint is swollen, erythematous, and tender
Interval gout	Asymptomatic period between attacks
Tophaceous gout	Deposits of monosodium urate crystals in soft tissues Complications include soft tissue damage, deformity, joint destruction, and nerve compression syndromes such as carpal tunnel syndrome
Atypical gout	Polyarthritis affecting any joint, upper or lower extremity May be confused with rheumatoid arthritis or osteoarthritis
Gouty nephropathy	Nephrolithiasis Acute and chronic kidney disease

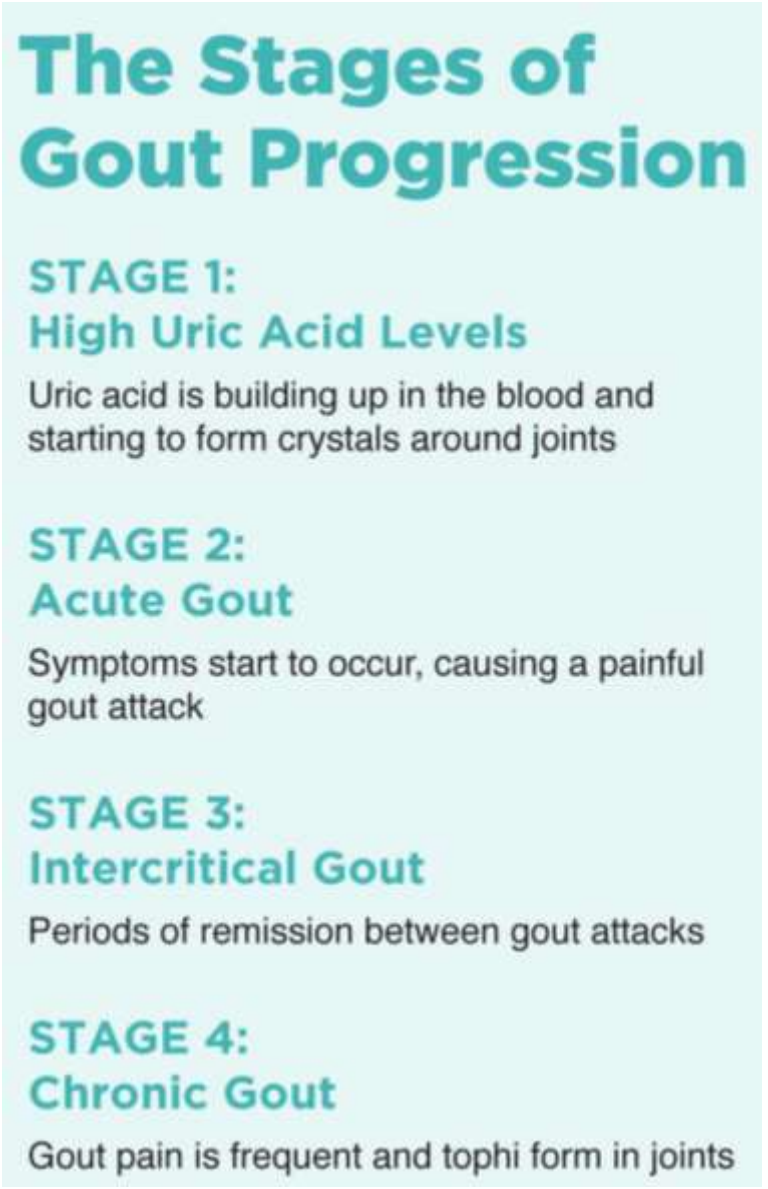
Presentation and diagnosis

- ✓ An acute attack of gout has a rapid onset, with pain being maximal at 6–24 h of onset and spontaneously resolving within several days or weeks.
- ✓ The first attack usually affects a single joint in the lower limbs in 85–90% of cases, most commonly the first metatarsophalangeal joint (big toe). Next most frequent joints: mid-tarsi, ankles, knees and arms.
- ✓ The affected joint is hot, red and swollen with shiny overlying skin. Even the touch of a sheet on the affected joint is too painful for the patient to bear.
- ✓ The patient may also have a fever, leucocytosis, raised ESR.
- ✓ The attack may also be preceded by prodromal symptoms as anorexia, nausea or change in mood.





- ✓ The gold standard for the diagnosis of gout is the demonstration of urate crystals in synovial fluid or in a tophus.
- ✓ Gout & septic arthritis may co-exist & in order to exclude septic arthritis synovial fluid is sent for Gram staining and culture.
- ✓ The course of gout follows a number of stages; initially, the patient may be asymptomatic with a raised serum uric acid level.
- ✓ Some patients may only ever experience 1 attack, but often a 2nd attack occurs within 6–12 months.
- ✓ Subsequent attacks tend to be of longer duration, affect more than one joint and may spread to the upper limbs.
- ✓ Untreated disease can result in chronic tophaceous gout, with persistent low-grade inflammation in a number of joints resulting in joint damage and deformity.



- ✓ Tophi deposition can occur anywhere in the body, but they are commonly seen on the helix of the ear, within and around the toe or finger joints, on the elbow, around the knees or on the Achilles tendons.

CLINICAL PRESENTATION — Acute Gouty Arthritis

General

- Gout classically presents as an acute inflammatory monoarthritis. The first metatarsophalangeal joint is often involved ("podagra"), but any joint of the lower extremity can be affected and occasionally gout will present as a monoarthritis of the wrist or finger. The spectrum of gout also includes nephrolithiasis, gouty nephropathy, and aggregated deposits of sodium urate (tophi) in cartilage, tendons, synovial membranes, and elsewhere.

Signs and Symptoms

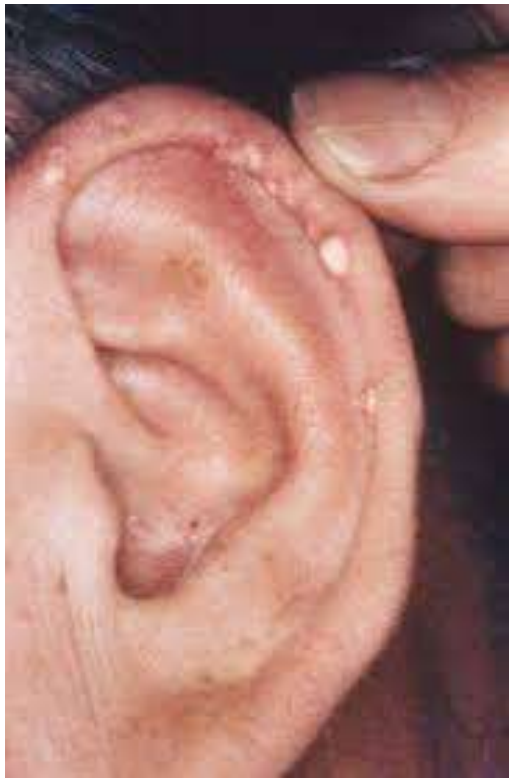
- Fever, intense pain, erythema, warmth, swelling, and inflammation of involved joints.

Laboratory Tests

- Elevated serum uric acid concentrations; leukocytosis.

Other Diagnostic Tests

- Observation of MSU crystals in synovial fluid or a tophus.
- For patients with long-standing gout, radiographs may show asymmetric swelling within a joint or subcortical cysts without erosions.



Treatment

- ✓ The management of gout can be split into the rapid resolution of the initial acute attack and long-term measures to prevent future episodes.

- ✓ Gout is often associated with other medical problems including obesity, hypertension, excessive alcohol and the metabolic syndrome of insulin resistance, hyperinsulinaemia, impaired glucose intolerance and hypertriglyceridaemia. This contributes to the increased CV risk & deterioration of renal function seen in patients with gout.

- ✓ Management is not only directed at alleviating acute attacks and preventing future attacks, but also identifying and treating other co-morbid conditions as HTN and hyperlipidaemia.

- ✓ Pharmacological measures should be combined with non-pharmacological measures as weight loss, changes in diet, increased exercise and reduced alcohol consumption.

- ✓ The prior 2012 ACR Guidelines for the Management of Gout have been criticized due to low quality of evidence supporting treat-to-target recommendations.
- ✓ Since the 2012 ACR Guidelines for the Management of Gout were published, several clinical trials have been conducted that provide additional evidence regarding the management of gout, leading the ACR Guidelines Subcommittee to determine that new guidelines were warranted.
- ✓ The strength of each recommendation was rated as strong or conditional.
- ✓ Strong recommendations reflect decisions supported by moderate or high certainty of evidence where the benefits consistently outweigh the risks, and, with only rare exceptions, an informed patient and his or her provider would be expected to reach the same decision.
- ✓ Conditional recommendations reflect scenarios for which the benefits and risks may be more closely balanced and/or only low certainty of evidence or no data are available.
- ✓ As data continue to emerge supporting best practices in management, implementation of these recommendations will ideally lead to improved quality of care for patients with gout.

Management of an acute attack:

- ✓ Drugs used in the management of an acute attack include NSAIDs, colchicine and corticosteroids.
- ✓ Treatment should be continued until the attack is terminated, usually between 1 and 2 weeks.
- ✓ The affected joints should also be rested for 1–2 days and initially treated with ice which has a significant analgesic effect during an acute attack.
- ✓ A complete medication review should be performed, and ideally medication which is likely to have contributed to the attack discontinued.
- ✓ Losartan has been shown to have uricosuric properties and is a suitable agent in hypertensive patients with gout.
- ✓ In patients with HF, diuretics are often essential and cannot be discontinued.

- ✓ Allopurinol should not be commenced during an acute attack as it may prolong or precipitate another attack. However, in patients already established on allopurinol therapy, allopurinol should always be continued during the attack.

- ✓ Aspirin at analgesic doses should be avoided as it blocks urate secretion. The continuation or initiation of low-dose aspirin (75–150 mg/day) is recommended in patients with cardiac disease as the benefits outweigh the minimal effect on serum uric acid levels.

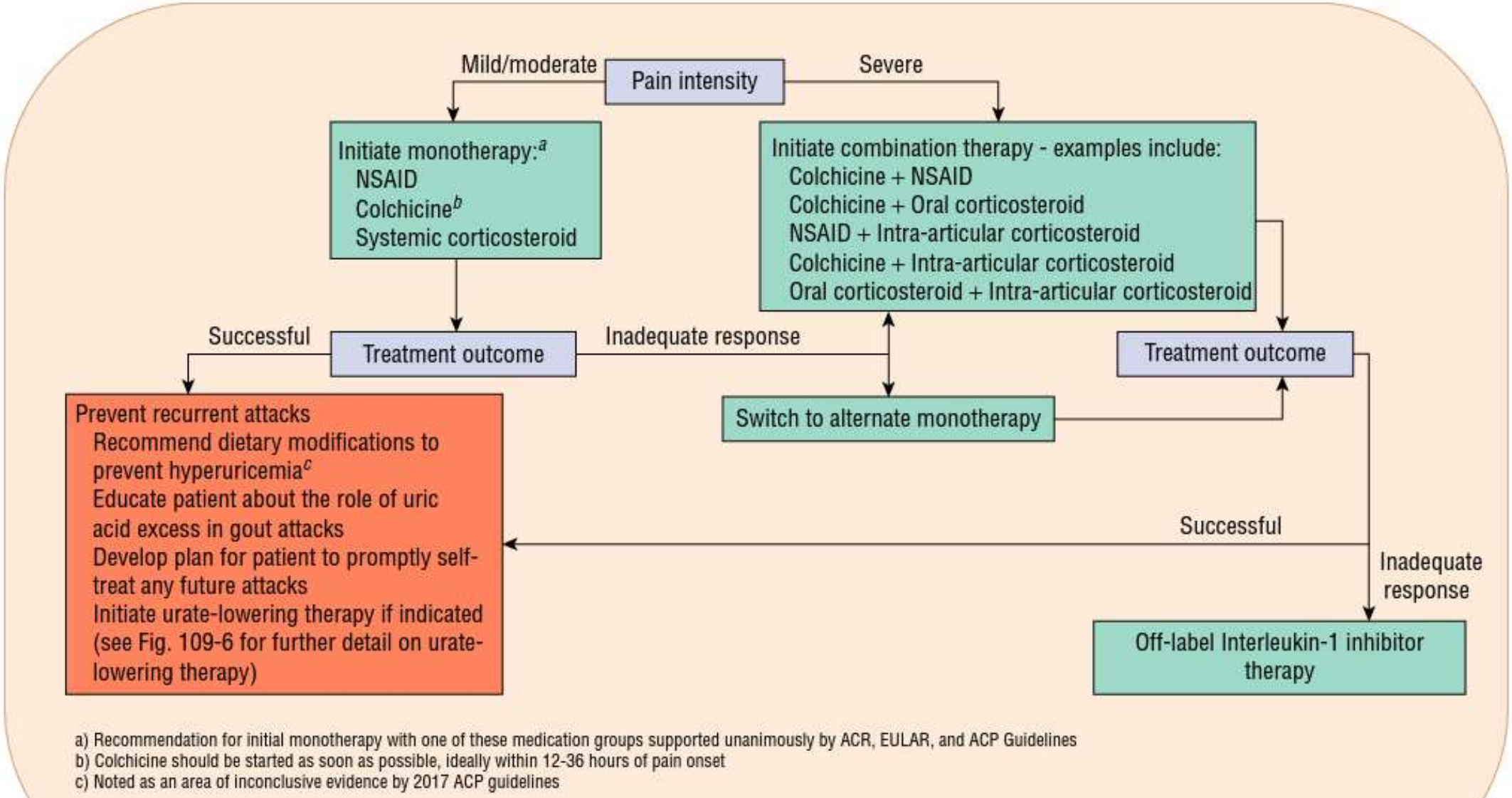
- ✓ Maximum doses of an NSAID should be commenced rapidly after the onset of an attack and then tapered 24 h after the complete resolution of symptoms. The usual treatment period is 1–2 weeks.

- ✓ Overall, there is no convincing evidence to promote the use of one NSAID over another in the management of acute gout.

- ✓ COX-2 selective agents are recommended for use in patients who are at high risk of developing GI side effects, but they are not recommended for routine use. It should be noted that the selective benefit of COX-2 inhibitors is lost in patients taking low dose aspirin.

- ✓ NSAIDs should be avoided in patients with HF, renal insufficiency and a history of gastric ulceration. Care should also be exercised in elderly patients with multiple pathologies.

- ✓ When prescribing an NSAID, the need for gastric protection should be considered in patients at increased risk of a peptic ulcer, bleed or perforation.



Algorithm for management of an acute gout attack. (Algorithm derived from 2017 ACP, 2016 EULAR and 2012 ACR gout guidelines.)

Table 6. Gout flare management*

Recommendation	PICO question	Certainty of evidence
For patients experiencing a gout flare, we strongly recommend using oral colchicine, NSAIDs, or glucocorticoids (oral, intraarticular, or intramuscular) as appropriate first-line therapy for gout flares over IL-1 inhibitors or ACTH (the choice of colchicine, NSAIDs, or glucocorticoids should be made based on patient factors and preferences). When colchicine is the chosen agent, we strongly recommend low-dose colchicine over high-dose colchicine given its similar efficacy and fewer adverse effects.	32	High†
For patients experiencing a gout flare for whom other antiinflammatory therapies are poorly tolerated or contraindicated, we conditionally recommend using IL-1 inhibition over no therapy (beyond supportive/analgesic treatment).	33	Moderate
For patients who may receive NPO, we strongly recommend glucocorticoids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH.	32	High†
For patients experiencing a gout flare, we conditionally recommend using topical ice as an adjuvant treatment over no adjuvant treatment.	31	Low

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; NSAIDs = nonsteroidal antiinflammatory drugs; IL-1 = interleukin-1; ACTH = adrenocorticotropic hormone; NPO = nothing by mouth (nulla per os).

† High quality of evidence from network meta-analyses supporting canakinumab, which has superior mean pain score reduction and mean day-2 joint tenderness reduction. However, the Voting Panel raised concern that the comparator was weak (triamcinolone 40 mg) and that cost issues significantly favor other agents.

- ✓ **Colchicine** has a slower onset of action than NSAIDs but is recommended in patients where NSAIDs are contraindicated.
- ✓ It should be started as soon as possible after the onset of an attack.
- ✓ A substantially lower dose of colchicine (1.2 mg initially, followed by a single 0.6mg dose one hour later) was as effective as higher doses traditionally used (continued hourly dosing until symptoms subside or GI symptoms become intolerable).
- ✓ Common side effects associated with colchicine are abdominal cramps, diarrhea, nausea, vomiting, and rarely bone marrow suppression, neuropathy and myopathy.
- ✓ Side effects are more common in patients with hepatic or renal impairment.
- ✓ Colchicine is metabolised by CYP3A4 and excreted by p-glycoprotein; toxicity can be caused by drugs that interact with its metabolism and clearance, and this includes macrolides, cyclosporin and protease inhibitors.

TABLE 109-8 Colchicine Dosing in Special Situations/ Colchicine Drug Interactions

	Treatment of Acute Gout Flares	Prophylaxis of Gout Flares
Impaired Kidney Function[a]		
Mild/moderate (creatinine clearance = 30-80 mL/min [0.5-1.33 mL/s])	Dose adjustment not required	Dose adjustment not required
Severe (creatinine clearance <30 mL/min [<0.5 mL/s])	Dose adjustment not required; treatment course should be repeated no more than once every 2 weeks	0.3 mg daily (starting dose)
Dialysis	Single 0.6-mg dose; treatment course should not be repeated more than once every 2 weeks	0.3 mg twice weekly (starting dose)
Hepatic Impairment[b]		
Mild/moderate	Dose adjustment not required	Dose adjustment not required
Severe	Dose adjustment not required; treatment course should be repeated no more than once every 2 weeks	Dose reduction should be considered

Colchicine Drug Interactions		
Strong CYP3A4 inhibitors • Atazanavir • Clarithromycin • Darunavir/ritonavir • Indinavir • Itraconazole • Ketoconazole • Lopinavir/ritonavir • Nefazodone • Nelfinavir • Ritonavir • Saquinavir • Telithromycin • Tipranavir/ritonavir	Single 0.6-mg dose followed by 0.3 mg 1 hour later; dose to be repeated no earlier than 3 days	0.3 mg once every other day to 0.3 mg once daily
Moderate CYP3A4 inhibitors • Amprenavir • Aprepitant • Diltiazem • Erythromycin • Fluconazole • Fosamprenavir • Grapefruit juice and related citrus products • Verapamil	Single 1.2-mg dose; dose to be repeated no earlier than 3 days	0.3-0.6 mg daily (0.6-mg dose may be given as 0.3 mg twice daily)
P-glycoprotein inhibitors • Cyclosporine • Ranolazine	Single 0.6-mg dose; dose to be repeated no earlier than 3 days	0.3 mg once every other day to 0.3 mg once daily

a Treatment of gout flares with colchicine is not recommended in patients with impaired kidney function who are receiving colchicine for prophylaxis.

b Treatment of gout flares with colchicine is not recommended in patients with hepatic impairment who are receiving colchicine for prophylaxis.

IV colchicine has resulted in fatalities and is no longer available.

- ✓ **Corticosteroids** are usually considered where use of an NSAID or colchicine is contraindicated or in refractory cases.

- ✓ They may be given intravenously, intramuscularly or direct into a joint (intra-articular) when only one or two joints are affected.

- ✓ In patients with a monoarthritis, an intra-articular corticosteroid injection is highly effective in treating an attack.

- ✓ Two different dosing strategies for oral corticosteroid therapy (prednisone or prednisolone) in the treatment of acute gout:
- 0.5 mg/kg daily for 5 to 10 days followed by abrupt discontinuation or
- 0.5 mg/kg daily for 2 to 5 days followed by tapering for 7 to 10 days

- ✓ A hypothetical risk exists for a rebound attack upon steroid withdrawal; therefore, gradual tapering is often employed when discontinuing steroid therapy.

- ✓ The adverse effects of corticosteroids are generally dose and duration dependent.

- ✓ **Interleukin-1 inhibitors:** IL-1β is critically associated with the inflammatory response induced by monosodium urate crystals.

- ✓ Anakinra and canakinumab, have demonstrated efficacy in the treatment of acute gout.

- ✓ The EULAR and ACR guidelines suggest that IL-1 inhibitors can be considered for treatment of severe acute gout attacks refractory to other treatments.

<u>Management of chronic gout:</u>

- ✓ The presence of hyperuricaemia is not an indication to commence prophylactic therapy.

- ✓ Some patients may only experience a single episode and a change in lifestyle, diet or concurrent medication may be sufficient to prevent further attacks.

- ✓ Patients who suffer one or more acute attacks within 12 months of the first attack should normally be prescribed prophylactic urate-lowering therapy.

- ✓ There are, however, some groups of patients where prophylactic therapy should be instigated after a single attack. These include individuals with uric acid stones, the presence of tophi at first presentation and young patients with a family history of renal or cardiac disease.

- ✓ Prophylactic treatment should not be initiated until an acute attack of gout has completely resolved.

- ✓ Once started, prophylactic treatment should be continued indefinitely even if further acute attacks develop.

- ✓ Drugs that lower serum uric acid can be classified into three groups according to their pharmacological mode of action.

- ✓ Xanthine oxidase inhibitors (allopurinol and febuxostat): xanthine oxidase catalyses the oxidation of hypoxanthine to xanthine and subsequently xanthine to uric acid.
- ✓ **Allopurinol** is the prophylactic agent of choice in the management of recurrent gout.
- ✓ In order to become pharmacologically active, allopurinol must be metabolised by the liver to oxypurinol. Oxypurinol has a much longer half-life than allopurinol, 14–16 h compared to 2 h.
- ✓ In patients with normal renal function, the starting dose is 100 mg/day; this is gradually increased in 100-mg increments every 2–5 weeks until the optimal serum urate level or the maximum dose is reached(maximum dose is 800 mg/day).
- ✓ A decrease in serum urate will occur within a couple of days of introducing allopurinol therapy with a peak effect at 7–10 days.
- ✓ The dissolution of tophi may take up to 6–12 months with effective therapy.

- ✓ Approximately 3–5% of patients treated with allopurinol suffer from an adverse reaction.
- ✓ Mild adverse effects as skin rash, leukopenia, GI problems, headache, and urticaria can occur with allopurinol administration.
- ✓ A more severe adverse reaction known as “allopurinol hypersensitivity syndrome”, which includes severe rash (toxic epidermal necrolysis, erythema multiforme, or exfoliative dermatitis), hepatitis, interstitial nephritis, and eosinophilia.
- ✓ Risk factors associated with the development of allopurinol hypersensitivity included female gender, age above 60 years, initial starting dose of allopurinol exceeding 100 mg/day, kidney disease, CV disease, and use of allopurinol for treatment of asymptomatic hyperuricemia.
- ✓ The dose of azathioprine or mercaptopurine should be reduced to approximately a quarter of the normal dose when co-prescribed with allopurinol.
- ✓ In addition, full blood counts should be performed at regular intervals to identify potential toxicity.

- ✓ **Febuxostat** is a more selective and potent inhibitor of xanthine oxidase than allopurinol and has no effect on other enzymes involved in purine or pyrimidine metabolism.
- ✓ It is licensed for the treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred including a history, or presence of, tophus and/or gouty arthritis.
- ✓ It is recommended as a secondline agent in patients who are intolerant of allopurinol or have C/Is
- ✓ The increased potency and good oral bioavailability of febuxostat leads to rapid decreases in serum uric acid levels permitting the testing of levels 2 weeks after starting therapy or adjusting the dose.
- ✓ Febuxostat should not be given to patients with IHD or CHF because of CV side effects.
- ✓ When initiating therapy with febuxostat, gout flare prophylaxis should be prescribed.
- ✓ The most common adverse effects include respiratory infection, diarrhea, headache and liver function abnormalities.

- ✓ The use of febuxostat is not recommended in patients concomitantly treated with mercaptopurine or azathioprine and theophylline, serum levels of theophylline should be monitored.
- ✓ Febuxostat is more effective than fixed-dose allopurinol 300 mg in lowering uric acid concentrations in trials of up to 40 months' duration. However, a reduction in the incidence of episodes of acute gout has not been demonstrated.
- ✓ **Uricosuric agents (probenecid & lesinurad)** increase uric acid excretion primarily by inhibiting post-secretory renal proximal tubular reabsorption of uric acid from filtered urate in the kidney.
- ✓ They are indicated as second-line agents in those who are urate under-excreters and are dependent on the patient having an adequate level of renal function.
- ✓ These agents should be avoided in patients with urate nephropathy or those who are over producers of uric acid due to the high risk of developing renal stones.
- ✓ Patients receiving a uricosuric agent are required to maintain an adequate fluid intake.

- ✓ **Probenecid** is given initially at a dose of 250 mg twice a day for 1 to 2 weeks and then 500 mg twice a day for 2 weeks. Thereafter, the daily dose is increased by 500-mg increments every 1 to 2 weeks until satisfactory control is achieved or a maximum dose of 2 g is reached.

- ✓ Probenecid can inhibit tubular secretion of other organic acids; so, increased plasma concentrations of penicillins, cephalosporins, sulfonamides, and indomethacin can occur.

- ✓ **Lesinurad** is approved as combination therapy with a xanthine oxidase inhibitor for treatment of hyperuricemia associated with gout in patients who have not achieved target serum UA concentrations with xanthine oxidase inhibitor monotherapy.

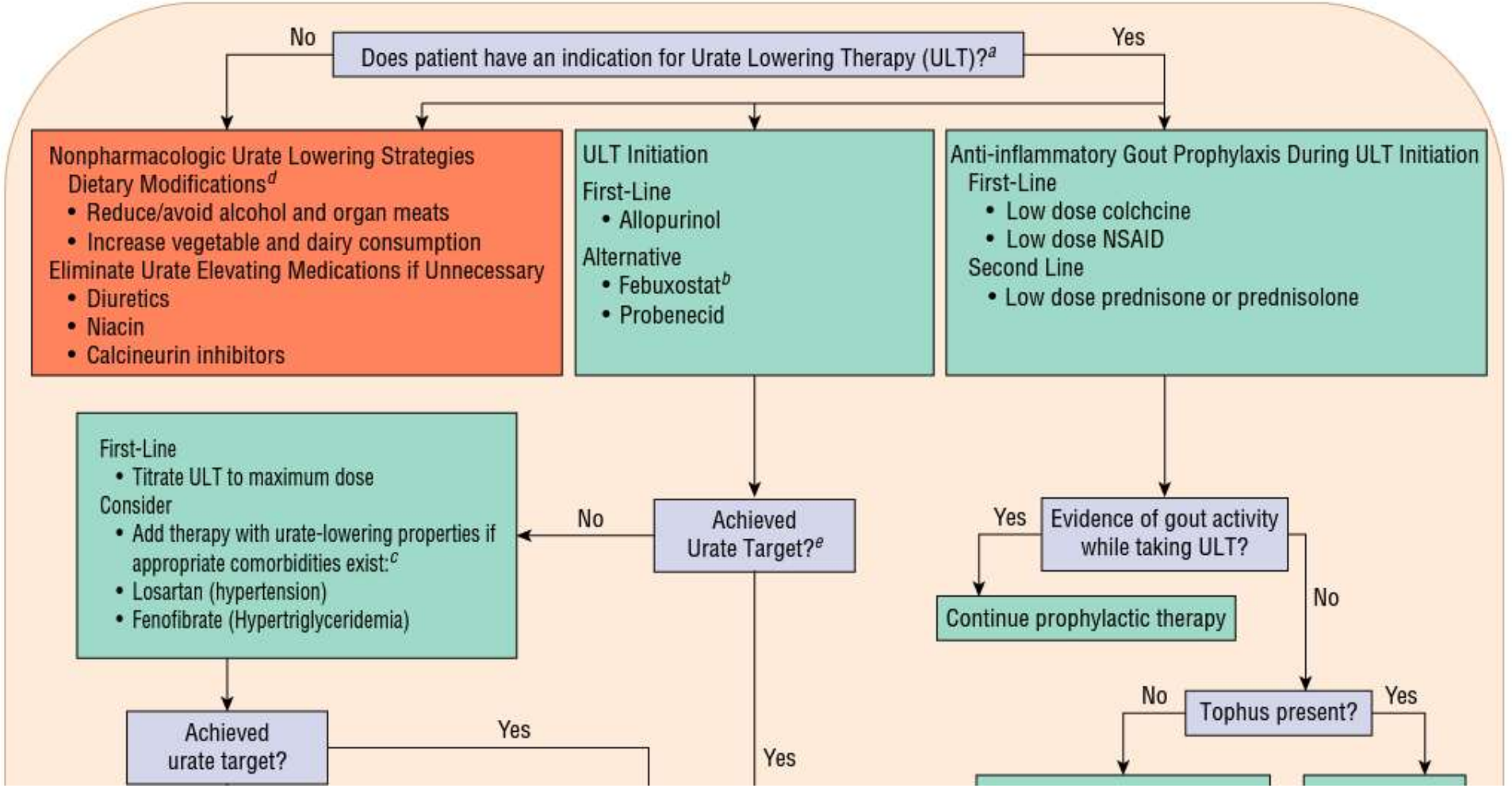
- ✓ Lesinurad carries a black box warning which highlights the increased risk of acute kidney injury when used in the absence of xanthine oxidase inhibitor therapy.

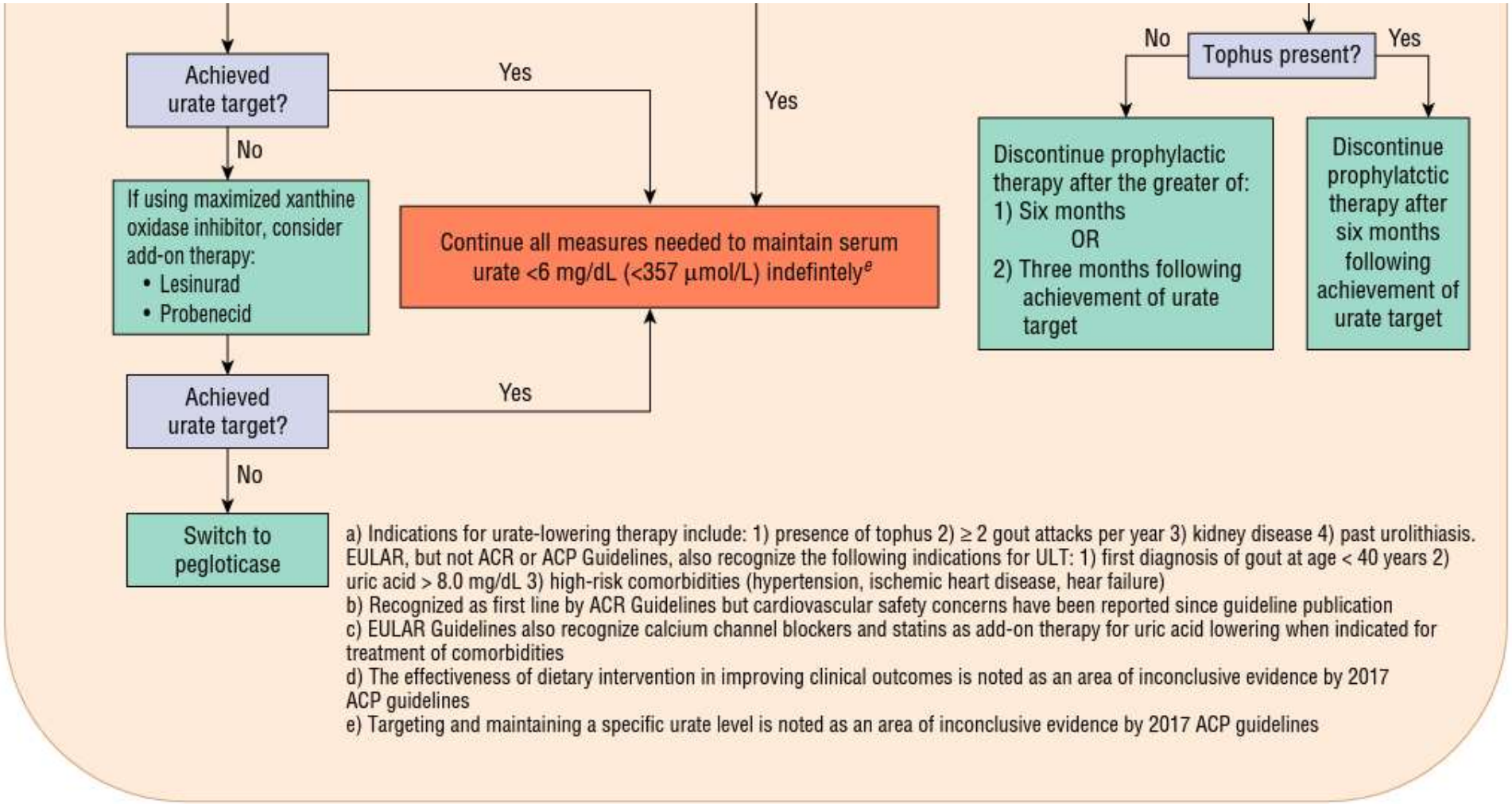
- ✓ The only approved dose of lesinurad is 200 mg daily due to increased risk of renal events when used at higher doses.

- ✓ Lesinurad should not be used in patients with creatinine clearance less than 45 mL/ min.

- ✓ **Pegloticase (PEG-uricase):** is a pegylated, recombinant form of uricase.
- ✓ It works to reduce serum uric acid by converting uric acid to allantoin, a water-soluble and easily excreted substance.
- ✓ It has demonstrated efficacy in reducing serum UA and resolving tophi in patients with severe gout & hyperuricemia (UA $\geq$ 8 mg/dL) who have failed or have a contraindication to other ULT.
- ✓ The IV infusions of pegloticase must be given over no less than 2 hours every 2 weeks, a potential inconvenience to many patients.
- ✓ The use of PEG-uricase has been associated with severe infusion reactions in a small minority of patients; this and its high cost are likely to limit its use.
- ✓ Immunogenicity issues associated with pegloticase therapy may limit the duration with which pegloticase therapy may be used effectively (pegloticase antibodies resulted in a loss of efficacy by month 4).

Algorithm for management of hyperuricemia in gout. (Algorithm derived from 2017 ACP, 2016 EULAR and 2012 ACR gout guidelines.)





a) Indications for urate-lowering therapy include: 1) presence of tophus 2) ≥ 2 gout attacks per year 3) kidney disease 4) past urolithiasis. EULAR, but not ACR or ACP Guidelines, also recognize the following indications for ULT: 1) first diagnosis of gout at age < 40 years 2) uric acid > 8.0 mg/dL 3) high-risk comorbidities (hypertension, ischemic heart disease, hear failure)
b) Recognized as first line by ACR Guidelines but cardiovascular safety concerns have been reported since guideline publication
c) EULAR Guidelines also recognize calcium channel blockers and statins as add-on therapy for uric acid lowering when indicated for treatment of comorbidities
d) The effectiveness of dietary intervention in improving clinical outcomes is noted as an area of inconclusive evidence by 2017 ACP guidelines
e) Targeting and maintaining a specific urate level is noted as an area of inconclusive evidence by 2017 ACP guidelines

Table 1. Indications for pharmacologic urate-lowering therapy (ULT)*

Recommendation	PICO question	Certainty of evidence
For patients with 1 or more subcutaneous tophi, we strongly recommend initiating ULT over no ULT.	1	High
For patients with radiographic damage (any modality) attributable to gout, we strongly recommend initiating ULT over no ULT.	2	Moderate
For patients with frequent gout flares (≥2/year), we strongly recommend initiating ULT over no ULT.	3	High
For patients who have previously experienced >1 flare but have infrequent flares (<2/year), we conditionally recommend initiating ULT over no ULT.	4	Moderate
For patients experiencing their first flare, we conditionally recommend *against* initiating ULT over no ULT, with the following exceptions.	5	Moderate
For patients experiencing their first flare and CKD stage ≥3, SU >9 mg/dl, or urolithiasis, we conditionally recommend initiating ULT.	5	Very low
For patients with asymptomatic hyperuricemia (SU >6.8 mg/dl with no prior gout flares or subcutaneous tophi), we conditionally recommend *against* initiating any pharmacologic ULT (allopurinol, febuxostat, probenecid) over initiation of pharmacologic ULT.	57	Hight

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; CKD = chronic kidney disease; SU = serum urate.
† There is randomized clinical trial data to support the benefit that ULT lowers the proportion of patients who develop incident gout. However, based on the attributable risk, 24 patients would need to be treated for 3 years to prevent a single (incident) gout flare leading to the recommendation against initiating ULT in this patient group.

Table 2. Recommendations for choice of initial urate-lowering therapy (ULT) in patients with gout*

Recommendation	PICO question	Certainty of evidence
For patients starting any ULT, we strongly recommend allopurinol over all other ULT as the preferred first-line agent for all patients, including in those with CKD stage ≥3.	10	Moderate
We strongly recommend a xanthine oxidase inhibitor over probenecid for those with CKD stage ≥3.		
For allopurinol and febuxostat, we strongly recommend starting at a low dose with subsequent dose titration to target over starting at a higher dose (e.g., ≤100 mg/day [and lower in patients with CKD] for allopurinol or ≤40 mg/day for febuxostat).	7	Moderate
For probenecid, we conditionally recommend starting at a low dose (500 mg once or twice daily) with dose titration over starting at a higher dose.		
We strongly recommend initiating concomitant antiinflammatory prophylaxis therapy (e.g., colchicine, NSAIDs, prednisone/prednisolone) over no antiinflammatory prophylaxis. The choice of specific antiinflammatory prophylaxis should be based upon patient factors.	9	Moderate
We strongly recommend continuing prophylaxis for 3–6 months rather than <3 months, with ongoing evaluation and continued prophylaxis as needed if the patient continues to experience flares.	9	Moderate
When the decision is made that ULT is indicated while the patient is experiencing a gout flare, we conditionally recommend starting ULT during the gout flare over starting ULT after the gout flare has resolved.	6	Moderate
We strongly recommend *against* pegloticase as first-line therapy.	10	Moderate†

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; CKD = chronic kidney disease; NSAIDs = nonsteroidal antiinflammatory drugs.
† Moderate evidence is in support of the efficacy of pegloticase, but due to cost, safety concerns, and favorable benefit-to-harm ratios of other untried treatment options, the recommendation is *against* using pegloticase as first-line agent.

When the decision is made that ULT is indicated while the patient is experiencing a gout flare, we conditionally recommend starting ULT during the gout flare over starting ULT after the gout flare has resolved.	6	Moderate

Starting ULT during a flare has conceptual benefits, including the time efficiency offered by initiating therapy during the concurrent flare visit rather than risking the patient not returning for ULT initiation. Furthermore, input from the **Patient Panel** emphasized that patients are likely to be highly motivated to take ULT due to the symptoms related to the current flare. However, concerns about starting ULT during a flare include potential *extension or worsening of a flare*, as well as the possibility of *information overload* for patients, which may lead to conflating flare management and long-term ULT. Two small RCTs and an observational study support the hypothesis that starting ULT during a flare does not significantly extend flare duration or severity. Input from the **Patient Panel**, citing their own ability to simultaneously process information related to flare treatment and ULT initiation together, along with their preference to start on a treatment path sooner to prevent future flares, **influenced the final recommendation**. As with all conditional recommendations, there may be patient factors or preferences that would **reasonably support the alternative** of delaying ULT initiation until the flare has resolved.

Table 3. Recommendations for all patients taking urate-lowering therapy (ULT)*

Recommendation	PICO question	Certainty of evidence
For all patients taking ULT, we strongly recommend a treat-to-target strategy of ULT dose management that includes dose titration and subsequent dosing guided by serial SU values to achieve an SU target over a fixed, standard-dose ULT strategy.	13	Moderate
For all patients taking ULT, we strongly recommend continuing ULT to achieve and maintain an SU target of <6 mg/dl over no target	14	High
For all patients taking ULT, we conditionally recommend delivery of an augmented protocol of ULT dose management by nonphysician providers to optimize the treat-to-target strategy that includes patient education, shared decision-making, and treat-to-target protocol.	8	Moderate
We conditionally recommend continuing ULT indefinitely over stopping ULT.	19	Very low

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; SU = serum urate.

Table 4. Recommendations for patients taking specific urate-lowering therapy (ULT) medications*

Recommendation	PICO question	Certainty of evidence
Allopurinol		
We conditionally recommend testing HLA–B*5801 prior to starting allopurinol for patients of Southeast Asian descent (e.g., Han Chinese, Korean, Thai) and African American patients, who have a higher prevalence of HLA–B*5801.	12	Very low
We conditionally recommend *against* HLA–B*5801 testing in all others.		
For patients with a prior allergic response to allopurinol who cannot be treated with other oral ULT, we conditionally recommend using allopurinol desensitization.	23	Very low
Febuxostat		
For patients with gout taking febuxostat with a history of CVD or a new CV event, we conditionally recommend switching to an alternative ULT agent if available and consistent with other recommendations in this guideline.	22	Moderate
Uricosurics		
For patients considered for, or taking uricosuric treatment, prior to starting any uricosuric treatment, we conditionally recommend *against* checking urinary uric acid over checking urinary uric acid.	28	Very low
For patients taking uricosuric treatment, we conditionally recommend *against* alkalinizing urine.	29	Very low

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; CVD = cardiovascular disease.

Table 5. When to consider switching to a new urate-lowering therapy (ULT) strategy*

Recommendation	PICO question	Certainty of evidence
For patients with gout taking their first XOI monotherapy at maximum-tolerated or FDA-indicated dose who are not at SU target and/or have continued frequent gout flares or nonresolving subcutaneous tophi, we conditionally recommend switching the first XOI to an alternate XOI agent over adding a uricosuric agent.	24	Very low
For patients with gout where XOI, uricosurics, and other interventions have failed to achieve SU target and who have frequent gout flares or nonresolving subcutaneous tophi, we strongly recommend switching to pegloticase over continuing current ULT.†	27	Moderate
For patients with gout for whom XOI, uricosurics, and other interventions have failed to achieve serum urate target and who have infrequent gout flares (<2 flares/year) and no tophi, we strongly recommend *against* switching to pegloticase over continuing current ULT.‡	27	Moderate

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes; XOI = xanthine oxidase inhibitor; FDA = Food and Drug Administration.
† There is moderate certainty of evidence about the efficacy of the benefits, harms, and high certainty about the costs of pegloticase. For patients with high disease activity, the magnitude of potential benefits outweighs the harms and costs of the drug.
‡ For patients with minimal disease activity, the smaller potential benefits do not outweigh the harms and costs of the drug.

✓ **Preventing gout flare:**

- It is important to inform patients about the disease, its curable nature, the aims of drug therapy and how to prevent and handle flares.
- The need for dietary and lifestyle changes should also be stressed.
- In over-weight patients, gradual weight loss should be encouraged.
- Low purine diets are difficult to adhere to.
- The importance of avoiding or reducing alcohol consumption should also be emphasised.
- The patient should be clear on what dose to take, when to initiate therapy, how long to take the medication for and any possible side effects to look out for.
- The patient should also be advised to avoid certain OTC medicines which may exacerbate an attack as the use of aspirin as an analgesic.
- Those taking long-term prophylactic therapy need to understand the importance of continuing therapy despite being asymptomatic.
- They should avoid running out of medication, as a short gap in therapy may precipitate an attack.
- Patients receiving uricosuric agents should be advised to maintain a fluid intake of at least 2 L/day to reduce the risk of uric acid stone formation in the kidneys.

Table 7. Management of lifestyle factors*

Recommendation	PICO question	Certainty of evidence
For patients with gout, regardless of disease activity, we conditionally recommend limiting alcohol intake.	41	Low
For patients with gout, regardless of disease activity, we conditionally recommend limiting purine intake.	42	Low
For patients with gout, regardless of disease activity, we conditionally recommend limiting high-fructose corn syrup.	43	Very low
For overweight/obese patients with gout, regardless of disease activity, we conditionally recommend weight loss.	46	Very low
For patients with gout, regardless of disease activity, we conditionally recommend *against* adding vitamin C supplementation.	48	Low

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes.

Table 8. Management of concurrent medications*

Recommendation	PICO question	Certainty of evidence
For patients with gout, regardless of disease activity, we conditionally recommend switching hydrochlorothiazide to an alternate antihypertensive when feasible.	47	Very low
We conditionally recommend choosing losartan preferentially as an antihypertensive when feasible.	47	Very low
We conditionally recommend *against* stopping low-dose aspirin (in those who are taking this medication for appropriate indications).	47	Very low
We conditionally recommend *against* adding or switching to fenofibrate	47	Very low

Strongly recommend | Conditionally recommend | Strongly recommend against | Conditionally recommend against

* PICO = population, intervention, comparator, outcomes.

✓ Evaluation of Therapeutic Outcomes:

- Baseline blood work for patients receiving hypouricemic medications chronically should include kidney function, liver enzymes, CBC, and electrolytes.

- During titration of ULT, uric acid should be monitored every 2 to 5 weeks; once the urate target is achieved, uric acid should be monitored every 6 months.

- Because of the high rates of comorbidities associated with gout, including DM, CKD, HTN, obesity, MI, HF, and stroke, elevated uric acid concentrations or gout should prompt evaluations for signs of CV disease and the need for appropriate risk reduction measures.

TABLE 109-7 Drug Monitoring

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
NSAIDs	Impaired kidney function (acute and chronic [Chapter 61], gastritis (worse with concurrent aspirin), fluid retention, blood pressure elevation	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Blood pressure Kidney function Edema Dark stools	Avoid for patients with peptic ulcer disease, active bleeding Use caution in congestive heart failure, dehydration, impaired kidney function Consider coadministration with a proton-pump inhibitor when used long term for patients at risk for GI bleeding
Systemic corticosteroids	GI upset, increased appetite, nervousness/restlessness, transient glucose intolerance, fluid retention, blood pressure elevation	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Glucose levels in patients with diabetes	Limit duration of therapy in patients with diabetes
Intra-articular corticosteroids	Injection pain, rebound arthritis	Therapeutic Resolution of pain Toxic Signs of rebound arthritis (pain relief followed by reemergence of pain)	Avoid if joint sepsis cannot be ruled out
Corticotropin	Increased appetite, nervousness/restlessness, transient glucose intolerance, fluid retention, blood pressure elevation	Therapeutic Resolution of pain	Requires intact pituitary–adrenal axis Less effective for patients receiving long-term oral corticosteroid therapy

Colchicine	Dose-dependent GI adverse effects (diarrhea, nausea, vomiting), rare myelosuppression, and reversible neuromyopathy	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic GI symptoms Complete blood count	
Interleukin-1 inhibitors	Injection site reaction, neutropenia, immune hypersensitivity reaction, infectious disease, malignancy	Therapeutic Resolution of pain Avoidance of gout attacks when used for prophylaxis Toxic Neutrophil count (prior to initiation, monthly for the first 3 months of therapy then after 6, 9, and 12 months of therapy) Temperature (periodically to detect infection)	Safety for use in acute gout and gout prophylaxis during initiation of urate-lowering therapy has not yet been established; not FDA approved for use in gout
Allopurinol	Rash, potential for fatal hypersensitivity syndrome	Therapeutic Serum urate level Reduced frequency of gout attacks Toxic Rash Kidney function	Can be used in both urate overproduction and urate underexcretion
Febuxostat	Liver enzyme elevation, nausea, arthralgias, rash, cardiovascular risk	Therapeutic Serum urate level Reduced frequency of gout attacks Toxic Liver function tests Kidney function	Can be used in both urate overproduction and urate underexcretion

Probenecid	Urolithiasis	Therapeutic Serum urate level Reduced frequency of gout attacks Toxic Kidney function	Useful in urate underexcretion Avoid for patients with history of urolithiasis
Pegloticase	Acute gout attack during treatment initiation, anaphylaxis, GI symptoms (constipation, nausea, vomiting), chest pain, nasopharyngitis	Therapeutic Serum urate levels Reduced frequency of gout attacks Toxic Signs/symptoms of anaphylaxis following infusion	Reserved for patients with gout refractory to conventional therapies Can be used in both urate overproduction and urate underexcretion
Lesinurad	Acute gout attack during treatment initiation, headache, GERD, acute kidney injury, major adverse cardiovascular events have been observed, although a causal relationship has not been established	Therapeutic Serum urate levels Reduced frequency of gout attacks Toxic Kidney function	Reserved for patients with hyperuricemia associated with gout who do not achieve target serum uric acid levels with conventional therapies Can be used in both urate overproduction and urate underexcretion Must be used in combination with a xanthine oxidase inhibitor due to increased risk of acute kidney injury with monotherapy

FDA, Food and Drug Administration; GERD, gastroesophageal reflux disease; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

TABLE 109-9 Pharmacotherapy Considerations in Gout

Conditions and Situations	Limitations to Pharmacotherapy	Alternative Therapies
Impaired Kidney Function	NSAIDs may lead to exacerbation of kidney impairment	Consider reduced-dose colchicine or corticosteroids for short-term treatment of acute gout Consider reduced-dose colchicine for prophylaxis during initiation of urate-lowering therapy
	Uricosuric therapy is ineffective in patients with impaired kidney function	Consider allopurinol or febuxostat
	Lesiurad is not indicated in patients with impaired kidney function	Consider allopurinol or febuxostat for first-line urate lowering therapy; consider pegloticase for refractory cases
GI disease	Colchicine may cause GI upset and diarrhea	Consider corticosteroids for treatment of acute gout If monoarticular, consider joint injection
	NSAIDs may cause GI bleeding or ulceration	Consider gastroprotection with coadministration of proton-pump inhibitor when NSAID therapy is used Consider colchicine or corticosteroids for treatment of acute gout Consider low-dose colchicine for prophylaxis during initiation of urate-lowering therapy
Congestive heart failure	NSAIDs may cause a congestive heart failure exacerbation	Consider colchicine for treatment of acute gout Consider colchicine for prophylaxis during initiation of urate-lowering therapy
	Concurrent use of diuretic may increase serum urate	If diuretic remains necessary, consider initiating urate-lowering therapy Consider losartan as a therapy for congestive heart failure given its uricosuric properties

Hypertension	Diuretics may increase uric acid	Consider losartan as alternative or additional antihypertensive therapy given its uricosuric properties Consider addition of urate-lowering therapy if diuretic remains necessary
	NSAIDs may worsen blood pressure control	Consider colchicine or corticosteroids for treatment of acute gout Consider colchicine for prophylaxis during initiation of urate-lowering therapy
Polypharmacy	CYP3A4 inhibitors and P-glycoprotein inhibitors interact with colchicine leading to elevated colchicine levels	Reduce the dose of colchicine used for the treatment and prophylaxis of acute gout Consider NSAIDs or corticosteroids for treatment of acute gout Consider NSAIDs for prophylaxis during initiation of urate-lowering therapy
	Added pharmacotherapy may be undesirable in a patient with a large medication burden	Consider losartan as urate-lowering therapy in patients with comorbid hypertension Consider fenofibrate as urate-lowering therapy in patients with hypertriglyceridemia
Financial limitations	Febuxostat and colchicine are considerably more costly compared with other gout treatments	Consider allopurinol as urate-lowering therapy Consider NSAIDs or corticosteroids for treatment of acute gout Consider NSAIDs for prophylaxis of gout during initiation of urate-lowering therapy

CYP, cytochrome P450; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

Starting from this slide, material is just for your own knowledge.

TABLE 109-6 Pharmacotherapy of Acute Gout, Anti-Inflammatory Prophylaxis during Initiation of Urate-Lowering Therapy and Hyperuricemia in Gout[a]

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Acute Gout					
NSAIDs					In general, not recommended in patients with advanced kidney disease as NSAID use may decrease kidney function; use with caution in patients with mild-to-moderate kidney impairment
Etodolac	Lodine, various	300 mg twice daily	300-500 mg twice daily		
Fenoprofen	Nalfon, various	400 mg three times daily	400-600 mg three to four times daily		
Ibuprofen	Advil, various	400 mg three times daily	400-800 mg three to four times daily		
Indomethacin	Indocin	50 mg three times daily	50 mg three times daily initially until pain is tolerable then rapidly reduce to complete cessation		
Ketoprofen	Orudis, various	75 mg three times daily or 50 mg four times daily	50-75 mg three to four times daily	Severe kidney impairment (GFR <25 mL/min [0.42 mL/s]): 100 mg maximum daily dose Mildly impaired kidney function: 150 mg maximum daily dose Impaired liver function with serum albumin <3.5 g/dL (<35 g/L): 100 mg maximum daily dose	

Naproxen	Naprosyn, various	750 mg followed by 250 mg every 8 hours until the attack has subsided		Not recommended in severe kidney impairment (creatinine clearance <30 mL/min [<0.5 mL/s])	
Piroxicam	Feldene	20 mg once daily or divided twice daily			
Sulindac	Clinoril	200 mg twice a day	150-200 mg twice daily for 7-10 days		
Meloxicam	Mobic	5 mg daily	7.5-15 mg daily	Not recommended if creatinine clearance <15 mL/min	
Celecoxib	Celebrex	800 mg followed by 400 mg on day one then 400 mg twice daily for 1 week			Option for patients with GI contraindications to nonselective NSAIDs; unclear risk-to-benefit ratio at this time due to cardiovascular concerns
Oral colchicine	Colcrys	1.2 mg initially, followed by 0.6 mg 1 hour later		See Table 109-8	Dose adjustment recommended when used with selected CYP3A4 and P-glycoprotein inhibitors
Corticosteroids					
Oral		0.5 mg/kg prednisone equivalent daily for 5-10 days followed by discontinuation or 0.5 mg/kg daily for 2-5 days followed by tapering for 7-10	30-60 mg prednisone equivalent once daily for 3-5 days, then taper in 5-mg decrements spread over 10-14 days until discontinuation		The use of an oral methylprednisolone dose pack may be considered

		days		
Intramuscular		Triamcinolone acetonide 60 mg IM once; methylprednisolone 100 mg IM once	Triamcinolone acetonide 60 mg IM once; methylprednisolone 100-150 mg IM daily for 1-2 days	Administration of intramuscular triamcinolone is to be followed by oral prednisone or prednisolone
Intra-articular	Kenalog	Triamcinolone acetonide 10 mg (large joints), 5 mg (small joints)	Triamcinolone acetonide 10-40 mg (large joints), 5-20 mg (small joints)	Intra-articular administration is acceptable when only one to two joints involved and should be used in combination with NSAIDs, colchicine, or oral corticosteroids

(*Continued*)

TABLE 109-6 Pharmacotherapy of Acute Gout, Anti-Inflammatory Prophylaxis during Initiation of Urate-Lowering Therapy and Hyperuricemia in Gout[a] (*Continued*)

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Corticotropin	H.P. Acthar Gel	40 units IM or SC every 72 hours	40-80 units IM or SC every 24-72 hours		Contraindicated for IV administration
Interleukin-1 inhibitors					Reserve use for refractory cases; use for gout is an off-label indication
Anakinra	Kineret	100-mg SC daily for 3 days			
Canakinumab	Ilaris	Single dose 150-mg SC			
Anti-Inflammatory Prophylaxis During Initiation of Urate-Lowering Therapy					
NSAIDs			Lowest effective dosage		
Oral colchicine	Colcrys	0.6 mg daily	0.6 mg once or twice daily	See Table 109-8	
Prednisone or prednisolone		≤10 mg daily			Second-line therapy; recommended only if colchicine and NSAIDs are both contraindicated, ineffective, or not tolerated

Interleukin-1 inhibitors					Reserve use for refractory cases Studied for 16-week duration
Rilonacept	Arcalyst	320-mg loading dose followed by 160 mg weekly (SC)			
Canakinumab	Ilaris	Single SC dose (50-300 mg) or four times weekly SC dosing (50 mg—50 mg—25 mg—25 mg)			
Hyperuricemia in Gout					
Xanthine oxidase inhibitors					
Allopurinol	Lopurin, Zyloprim	100 mg daily	100-800 mg daily to achieve serum urate concentration <6 mg/dL (<357 μmol/L)	Start at dose of 50 mg daily for patients with a glomerular filtration rate <30 mL/min/1.73 m^2 (<0.29 mL/s/m^2)	

Febuxostat	Uloric	40 mg daily	40-80 mg/daily	No dosage adjustment necessary for patients with mild-to-moderate kidney impairment (creatinine clearance 30-89 mL/min [0.5-1.49 mL/s]) Insufficient data in patients with creatinine clearance <30 mL/min (<0.5 mL/s)	
Uricosurics					
Probenecid	Probalan	250 mg twice daily for 1 week	500-2,000 mg/day (target serum urate concentration <6 mg/dL [<357 mol/L])	Not recommended if creatinine clearance <50 mL/min (<0.83 mL/s)	
Lesinurad	Zurampic	200 mg once daily in combination with a xanthine oxidase inhibitor		Not recommended if creatinine clearance <45 mL/min (<0.75 mL/s) Not studied in patients with severe hepatic disease Contraindicated in tumor lysis syndrome and Lesch-Nyhan syndrome	Should be used in combination with a xanthine oxidase inhibitor due to increased risk of acute kidney injury with lesinurad monotherapy Use is not recommended in patients taking allopurinol doses <300 mg daily (normal kidney function) or <200 mg daily (creatinine clearance <60 mL/min)

TABLE 109-6 Pharmacotherapy of Acute Gout, Anti-Inflammatory Prophylaxis during Initiation of Urate-Lowering Therapy and Hyperuricemia in Gout[a] (*Continued*)

Drug	Brand Name	Initial Dose	Usual Range	Special Population Dose	Other
Combination Therapy					
Lesinurad/ Allopurinol	Duzallo	Lesinurad 200 mg/ allopurinol 300 mg: one tablet daily		Lesinurad 200 mg/ allopurinol 200 mg: one tablet daily recommended if creatinine clearance is 45-60 mL/min Not recommended if creatinine clearance <45 mL/min (<0.75 mL/s)	See above for lesinurad and allopurinol comments
Other					
Pegloticase	Krystexxa	8 mg IV every 2 weeks			Optimal treatment duration has not been established

[a]Agents available in the United States.

CYP, cytochrome P; GFR, glomerular filtration rate; IM, intramuscular; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; SC, subcutaneous.

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1:33

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3:20