INTRODUCTION

Gout is an inflammatory arthritis caused by the deposition of monosodium urate (MSU) crystals in synovial fluid and in other tissues. It is also known as crystal arthritis and “the disease of kings.”1-4 The “disease of kings” sprang from the observation in pre-modern times that gout was largely a disease of the affluent, due to the association of consumption of rich foods (eg, meats, seafood) and alcohol with its symptoms.5 The word “Gout” is derived from the Latin word gutta (or ‘drop’) and stems from the medieval belief that the disease was caused by an imbalance of the body’s “humors,” some “dropping” into the afflicted joint, and conceptually not much different from our modern understanding of the mechanism. In addition, podagra, or gout of the foot or great toe is derived via Latin from Greek, from pous foot + agra a trap = foot trap or seizure.6

Gout is among the earliest diseases to be described by ancient physicians, first recorded by the Egyptians in 2640 BC. Descriptions are also given by Hippocrates (5th century BC) and Galen (2nd century AD) that remain with us today. The word “gout” was first used as a disease description by Randolphus of Bocking (1197-1258), a Dominican monk, who described podagra as gutta quam podagram vel artiticam vacant, or the gout that is called podagra or arthritis.6

If you have ever suffered from a gout attack, you are in good company as there have been, and are many prominent gout sufferers.7 They include Martin Luther, Francis Bacon, Michelangelo, Benjamin Franklin, Charles Darwin and Isaac Newton. In addition, the course of history has been altered due to poorly timed gout attacks in certain individuals. One supported legend is that William Pitt (1759-1806), a member of the British Parliament and a supporter of the colonies, was absent on several occasions due to severe gout. Had he been present for key debates and votes, the Boston Tea Party and perhaps the Battle of Bunker Hill may have been avoided.

ETIOLOGY AND PATHOPHYSIOLOGY

Gout is one of the most common forms of inflammatory arthritis in adults. The 2010 estimates for the United States are that 8.3 million people are affected (3.9%). This peaks for males at 70-79 years (10%) and ≥80 years for females (6%). There are clearly ramifications for an aging population.8,9

The underlying metabolic disruption necessary for the development of gout is too much uric acid in the blood (hyperuricemia). However, the presence of hyperuricemia does not necessarily equate with gout symptoms as hyperuricemic patients may be asymptomatic. Physiologically, the serum reaches supersaturation with monosodium urate at approximately 7 mg/dL (416 μmol/L) and the definition of hyperuricemia is a serum urate level of ≥6.8 mg/dL (404 μmol/L).1,8

Uric acid is a metabolic waste product from purines which are involved in the enzymatic processes of nucleic acid synthesis. In normal humans, excess uric acid is excreted out through the kidneys. Other mammals’ metabolism is capable of going one step farther and breaking down the uric acid to water soluble allantoin via an enzyme, uricase. A normal urate pool is approximately 1200 mg in men and 600 mg in women. Increases of this urate pool occur due to excess production or under excretion of uric acid.8,10

Overproduction: Uric acid is produced from purines from three sources: dietary purine, tissue nucleic acid to purine nucleotide conversion and de novo synthesis of purine bases. The average human produces about 600 to 800 mg of uric acid daily. Diet plays little role in the absence of metabolic disruption. There are two enzyme abnormalities that result in overproduction of uric acid. The first is an overactivity of phosphoribosyl pyrophosphate (PRPP) synthetase in the nucleic acid synthesis process and consequently causes an increased production of uric acid. The second abnormality is an enzyme deficiency, hypoxanthine-guanine phosphoribosyl-transferase (HGPRT) that causes a
shift of production to guanine and hypoxanthine which is then metabolized to uric acid. Of note is that there is a relatively rare condition of a complete absence of HGPRT that results in the Lesch-Nyhan syndrome, a childhood disease characterized by excessive production of uric acid in addition to choreoathetosis and mental retardation.8,10

The latter part of purine metabolism leads to the compounds hypoxanthine and to xanthine which then is metabolized to uric acid via xanthine oxidase. This is the first attack point for preventative therapy, inhibiting the xanthine oxidase and preventing the formation of uric acid. The other two major areas are after uric acid formation. The uricases breakdown uric acid to water-soluble allantoin and the uricosurics promote the excretion of uric acid. The agents for acute gout attacks all work to alleviate the inflammatory response of the uric acid crystallization in the joint space.3,8,10

Underexcretion: In the normal human uric acid is largely excreted through the kidney and a small amount through the gastrointestinal tract (approximately 2/3 and 1/3, respectively). Excretion through the kidney is not completely defined and involves several mechanisms of passive and active transport in the glomerulus. It is estimated that 80% to 90% of patients with gout have some disorder with the urinary excretion of uric acid.8

Therapeutic options for treatment of hyperuricemia/gout revolve around these two functions of overproduction or underexcretion of uric acid. Determination can be made by measuring the amount of uric acid excretion over 24 hours. This can be done on a purine-free diet for 3-5 days (preferred but very difficult to accomplish), or on a regular diet. On the purine-free diet, over-producers will excrete >600 mg uric acid, while underexcretors provide <600 mg. On a regular diet, excretion of >1000 mg over 24 hours are over-producers.8

**Risk factors:**1,2,8

**Drugs:** Thiazide diuretics, cyclosporine, ethambutol, pyrazinamide, levodopa, cytotoxic drugs, tacrolimus, ribavirin and interferon, teriparatide and aspirin (low dose, <1 g/day). However, even with small, cardioprotective doses of aspirin (75mg daily), the rate of uric acid excretion was decreased by 15% that resulted in a small but significant rise in serum uric acid concentrations. This decrease in uric acid clearance was observed within one week of initiating low-dose aspirin therapy. Although the increase was small a clinical risk/benefit assessment will be needed per patient.11

**Diet:** A high purine diet includes meat and seafood, alcohol (beer and liquors), soft drinks (with sugar) and fructose-containing food/drinks. Foods with a decreased risk include coffee, dairy products and vitamin C.

**Conditions:** insulin resistance, metabolic syndrome, obesity, renal insufficiency, hypertension, congestive heart failure, organ transplantation, hospitalization and surgery.

**Genetics:** Common genetic polymorphisms have been identified in several genes. Also, rare X-linked inborn errors of metabolism can cause gout.

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**CLINICAL PRESENTATION AND DIAGNOSIS**

“..."The patient goes to bed and sleeps quietly until about two in the morning when he is awakened by a pain which usually seizes the great toe, but sometimes the heel, the calf of the leg or the ankle. The pain resembles that of a dislocated bone … and this is immediately succeeded by a chilliness, shivering and a slight fever … the pain increases, which is mild in the beginning but grows gradually more violent every hour … so exquisite pain as not to endure the weight of the clothes nor the shaking of the room from a person walking briskly therein.” [Thomas Sydenham (1624-1689)]5,12

**DIAGNOSIS**

The diagnosis of gout is divided into primary and secondary. Primary gout is generally unrelated to an identifiable cause while secondary gout is related to a stimulating factor, such as drugs, concomitant disease or known genetic mutations. The most recent guidelines are from European League Against Rheumatism (EULAR) from 2006; their report is in two parts, addressing diagnosis and management recommendations.13,14 There are 10 diagnostic recommendations:13

1. “In acute attacks the rapid development of severe pain, swelling, and tenderness that reaches its maximum within just 6 to 12 hours, especially with overlying erythema, is highly suggestive of crystal inflammation though not specific for gout.

2. For typical presentations of gout (such as recurrent podagra with hyperuricaemia) a clinical diagnosis alone is reasonably accurate but not definitive without crystal confirmation.

3. Demonstration of monosodium urate (MSU) crystals in synovial fluid or tophus aspirates permits a definitive diagnosis of gout.

4. A routine search for MSU crystals is recommended in all synovial fluid samples obtained from undiagnosed inflamed joints.

5. Identification of MSU crystals from asymtomatic joints may allow definite diagnosis in intercritical periods.

6. Gout and sepsis may coexist, so when septic arthritis is suspected Gram staining and culture of synovial fluid should still be performed, even if MSU crystals are identified.

7. While being the most important risk factor for gout, serum uric acid levels do not confirm or exclude gout, as many people with hyperuricaemia do not develop gout, and during acute attacks serum levels may be normal.

8. Renal uric acid excretion should be determined in selected gout patients, especially those with a family history of young onset gout, onset of gout under age 25, or with renal calculi.

9. Although radiographs may be useful for differential diagnosis and may show typical features in chronic gout, they are not useful in confirming the diagnosis of early or acute gout.

10. Risk factors for gout and associated co-morbidity should be assessed, including features of the metabolic syndrome (obesity, hyperglycaemia, hyperlipidaemia, hypertension)."
DIFFERENTIAL DIAGNOSIS

The differential diagnosis of gout can be a significant exercise, at least on initial complaint and examination. Apart from recognizing that there are a variety of disorders that can present as gout, in the absence of an existing diagnosis, the pharmacist should refer patients to the physician for a definitive determination. Some of the conditions that need to be considered include: pseudogout (pyrophosphate crystal related arthritis), rheumatoid arthritis, seronegative inflammatory arthritis, septic arthritis, osteoarthritis, psoriatic arthritis, cellulitis, trauma or hemarthrosis and sarcoidosis.

ACUTE GOUTY ARTHRITIS

An acute gout attack classically occurs in the great toe (podagra) and then in order of frequency, the instep, ankle, heel, knee, wrist, fingers and elbow. There is acute pain in the affected joint accompanied by warmth, swelling and redness; there may also be a fever. The lower extremities are more commonly affected and this may be because temperatures are cooler, allowing crystallization of uric acid at lower concentrations. Multiple articular involvement is unusual and most commonly seen in the elderly. Acute attacks most typically occur late at night or early in the morning, also due to crystallization of uric acid, this time due to movement of water from the joint space while joints are resting.

Precipitating events of an acute gout attack include stress, trauma (eg, injury, surgery), alcohol ingestion and infection. Also included are rapid lowering of uric acid with drugs, either intentionally with treatment, or unintentionally with other agents (see Risk Factors). Untreated attacks will last 3 to 14 days without treatment.

KIDNEY DAMAGE

Uric acid nephrolithiasis can occur in approximately 10% of patients with gout. This should be suspected in any patient with hyperuricemia and kidney stones. Typically, uric acid stones are small, round and translucent on X-ray and are most common in overproducers of uric acid (>1000 mg/day excreted) with acidic urine (pH<6).

Renal failure can occur and is due to either acute gouty nephropathy (most commonly due to patients with myeloproliferative or lymphoproliferative disorders where there is massive cellular turnover due to the disease or subsequent chemotherapy), or chronic gouty nephropathy due to long term deposition of uric acid crystals in the renal parenchyma. The chronic form is associated with concomitant hypertension, diabetes mellitus and atherosclerosis.

TOPHACEOUS GOUT

The tophus is a chronic granulomatous lesion with a core of MSU and surrounded by soft connective tissue that form hard lumps, usually in and around affected joints but also in the helix of the ear. However, tophi deposition can occur nearly anywhere in the body. This is a characteristic of chronic gout. Tophi can be cosmetic problems and physical problems, if their formation impedes joint motion. It generally takes many years of hyperuricemia to form (5-20 years). Tophi formation in the finger pads is characteristic of elderly women with gout and taking diuretics. Tophi are generally painless and are rarely infected. They can be treated and dissolved with diligent hypouricemic therapy.

TREATMENT

Gout and Hyperuricemia

The primary aims of treatment of gout are to relieve the acute attack, prevent further attacks and prevent complications of crystal deposition. Table 1 presents the information on the available treatments for acute gout attacks and prevention of further gout attacks (intercritical gout).

Acute Gouty Arthritis

NSAIDs: The general flow of therapy for acute gout is initial treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). The four NSAIDs listed in Table 1 are the more common ones used. Indomethacin, naproxen and sulindac are the only ones that have a specific FDA indication for gout treatment, however, there appears to be no therapeutic difference in efficacy among any of the agents. This leaves room for patient preference. Indomethacin is perhaps the most commonly prescribed NSAID for gout and that may due to its earlier Food and Drug Administration (FDA) approval in 1965.

NSAIDs are not without risk. Caution should be used in patients with gastrointestinal bleeding or gastritis, renal dysfunction and fluid retention. Other cautions include use in patients with hypertension, heart failure, asthma and the elderly.

Colchicine is likely the oldest known and currently active therapy for gout. Sources vary but it has been in use at least since the 6th century AD. It is derived from the autumn crocus of the Lily family (Colchicum autumnale). Colchicine existed in the United States as an unapproved generic drug for many years until 2009 when the FDA formally approved a single product and prescribing information, Colcrys by URL Pharma. Based on studies by the company and other data the recommended dose of colchicine has changed to a more conservative, lower dose, 1.2 mg initially, then 0.6 mg one hour later. This is much lower than previously used doses. There have been many regimens published but most of them essentially dosed colchicine periodically (typically hourly) until symptom relief or toxicity (diarrhea, gastrointestinal distress) or a top dose of 8 mg. The new, lower dose appears to be as effective and much less toxic.

Corticosteroids are generally recommended when the NSAIDs or colchicine cannot be used. In the few comparative trials, oral corticosteroids appear relatively equal to NSAIDs (using prednisolone 30 to 35 mg). Monoarticular attacks can be treated with intra-articular injections. Systemic corticosteroids are most commonly used for multiple joint involvement. Corticosteroids are typically safe and effective with short term use but long term use can be problematic and should be avoided. Even short term use can alter control of hypertension and diabetes mellitus; it is also important to rule out septic arthritis before using these agents.
**Intercritical Gout**

Intercritical gout is the time between acute attacks. This is distinguished from asymptomatic hyperuricemia. As mentioned earlier, asymptomatic hyperuricemia does not require treatment, but once an acute attack has occurred, and other diagnostic criteria have been satisfied, then gout is diagnosed and the focus becomes lowering the serum uric acid to acceptable levels, generally less than 6 mg/dL. Some sources prefer less than 5 mg/dL and to dissolve tophi, serum uric acid levels of less than 4 to 5 mg/dL may be needed.1,3,8,9,15

**Lifestyle modifications** 1,3,8,10,15

Diet has long been associated with the development of gout attacks, perhaps among the earliest observations. A diet high in purine content (meat, seafood, some vegetables) and alcohol, especially beer has been thought to predispose to gout development. In addition, more recent evidence has also implicated high fructose foods, particularly soft drinks. Protective dietary components include coffee, dairy products, vitamin C and cherries. All protein sources are not equal and it appears the high purine vegetables and dairy products are not nearly as much of a problem as meats. A protective association is also present for a low body mass index (BMI) which simply adds a “healthy lifestyle” label to gout management. Unfortunately, a rigid low purine diet is generally unappetizing, very difficult to maintain for any length of time and only moderately effective.

Since there is the association of various cardiovascular and endocrine maladies with gout and the metabolic syndrome (includes dyslipidemias, hypertension, type 2 diabetes mellitus and obesity), a healthy lifestyle which includes a reasonable, balanced diet, zero to moderate alcohol use and appropriate exercise with a goal of a healthy BMI, is a good general recommendation for gout patients. In addition to a healthy diet, hydration is important for the patient with gout. This is especially true for the patient who has developed nephrolithiasis but also more generally to prevent such renal complications and crystallization of MSU. Some recommendations include maintaining a urine volume of 2 to 3 L per day.3,8

**Urate-lowering treatment**

The purpose of lowering serum uric acid is to prevent acute gouty attacks and long-term crystal deposition problems such as kidney stones and tophi. Urate-lowering therapy is generally considered when there are at least two gout attacks per year, or tophi development. Other factors such as acute attack severity, coexisting conditions (eg, kidney stones) and patient preference may also weigh on the decision. Urate-lowering therapy should begin 2 to 8 weeks after an acute attack (not during an attack).1,8 Doses are increased over a few weeks to months. Close monitoring should be done for serum uric acid, renal function and adverse events of the drugs.

There are three classes of urate-lowering drugs: The Xanthine Oxidase inhibitors which consist of allopurinol and febuxostat, and block the final metabolism of hypoxanthine and xanthine to uric acid; uricosuric agents which includes only probenecid and promote the excretion of uric acid through the kidney; and the newer uricase agents of which only pegloticase is approved for use in gout which directly breaks down uric acid to water soluble allantoin.

**Xanthine Oxidase Inhibitors**

Allopurinol is the most commonly prescribed drug of this class and was first approved for the market in 1966.1,21 It is a relatively well tolerated drug, and is the initial drug of choice for most patients in need of urate lowering therapy, but there are some issues with it. The recommended dosage begins with 100 mg/day and increases 100 mg/day at 2-4 week intervals. The most common dose is 300 mg/day, but the dosage range is up to 800 mg/day. Studies have shown that many patients are underdosed for the target uric acid serum level of 6 mg/dL and more patients should receive more than 300 mg/day. The dose should also be reduced for renal dysfunction (see table). Up to 5% of patients are unable to tolerate the drug.8

The most common side effect is mild pruritis/rash which occurs in up to 2% of patients. Asymptomatic liver function tests (LFTs) may also occur in approximately 5% of patients. However, a serious hypersensitivity reaction may occur in up to 0.4% of patients and it is fatal in 20-25% of these patients. Symptoms include a severe cutaneous reaction such as the Stevens-Johnson syndrome, eosinophilia, leukocytosis, fever, hepatitis and renal failure.1,2,3,8,9,15 There are some significant drug interactions with azathioprine, mercaptopurine, warfarin and ampicillin/amoxicillin.

Febuxostat (Uloric) was approved in 2009 and the first new drug for gout approved in 40 years.22 When the drug was first introduced, studies seemed to indicate that it may be more effective than allopurinol. However, upon further analysis, the doses used may not have been comparable, so the drugs are considered relatively equal in efficacy. The dose is initiated at 40 mg/day to a maximum of 80 mg/day in two weeks, and there is no adjustment needed for renal dysfunction. The most common adverse events include LFT abnormalities along with nausea, arthralgias and rash. In addition, there is some concern with cardiovascular thromboembolic effects, so patients should be monitored for signs and symptoms of myocardial infarction and stroke.23,24,25

Febuxostat is positioned as the alternative to allopurinol. It is recommended for those patients who are hypersensitive to, or intolerant of allopurinol or where allopurinol appears ineffective. Febuxostat, available only as the trade name Uloric, is significantly more expensive than allopurinol. One online pharmacy prices them as febuxostat 40 mg, 30 tablets, $192.40 and allopurinol 300 mg, 100 tablets, $23.99. This would make the daily costs of roughly comparable doses of febuxostat 40 mg/day and allopurinol 300 mg/ day $6.41 and $0.24, respectively.

**Uricosuric Agents**

Probenecid is the only available uricosuric product on the U.S. market. First approved in 1951 the original trade name,
Benemid is discontinued but is available as a generic product.\textsuperscript{28} Uricosurics are only indicated for underexcretors of uric acid.\textsuperscript{8,15} They act by blocking tubular reabsorption of uric acid in the kidney thus promoting excretion. Probenecid is ineffective in renal dysfunction, and uricosurics can promote development of kidney stones. Clinicians must also be concerned with urine pH (acid urine promotes stone formation) and adequate hydration. Also, probenecid must be dosed twice daily and there are numerous drug interactions. They have fallen out of favor for therapy, replaced largely by allopurinol.

### Uricase Agents

The uricase agents are an artificial enzyme that metabolizes uric acid to water-soluble allantoin that is easily excreted in the urine. There are two such products on the market: Pegloticase (Krysteexa) and rasburicase (Elitrek). Pegloticase is indicated for the treatment of chronic gout in adult patients refractory to conventional therapy.\textsuperscript{29} Rasburicase, although it acts in a similar fashion, is indicated for initial management of plasma uric acid levels in pediatric and adult patients with leukemia, lymphoma and solid tumor malignancies and receiving anticancer therapy expected to result in tumor lysis and subsequent elevation of plasma uric acid.\textsuperscript{30} Rasburicase would rarely be considered for use in a patient with gout due to its immunogenicity and its short half-life.\textsuperscript{1,3}

Pegloticase is the newest gout therapy, approved for the market in September 2010.\textsuperscript{31} It is a last line treatment, generally considered when all other uric acid-lowering therapies have failed or are not tolerated; its indication is for adult patient with chronic gout refractory to conventional therapy.\textsuperscript{29} It is a polyethylene glycol (PEG)-conjugated uricase with an 11 to 12 day half-life. While the therapy is intuitive, that is a direct elimination of the offending agent (uric acid), there are several drawbacks. It must be given intravenously. There is a significant incidence of infusion reactions (most commonly urticaria, chest discomfort/pain, erythema, pruritus, dyspnea – 26%) and severe allergic reactions (anaphylaxis – 5%).\textsuperscript{29,32} The manufacturer recommends pretreatment with antihistamines and corticosteroids.\textsuperscript{29} Most common are gout flares (77%) for which prophylactic therapy with NSAIDs or colchicine should be instituted, generally one week before therapy and then continued for six months. Also, a 2% incidence of exacerbation of pre-existing heart failure has been reported. The other drawback is cost. In 2011, the wholesale acquisition cost for an 8 mg vial was $2300.00.\textsuperscript{33} If regular therapy was need, the cost could become prohibitive.

### Other drugs \textsuperscript{1,3,8}

Losartan is an angiotensin II receptor antagonist and has shown benefit in lowering serum uric acid apparently by acting on its tubular reabsorption and promoting excretion. It may also help to alkalinize the urine. It does not appear to be a class effect.

Fenofibrate, a fibrac acid agent appears to act by promoting clearance of hypoxanthine and xanthine, the precursors to uric acid.

Both of these agents can promote a significant reduction in serum uric acid but do not appear to be capable of acting as primary agents. Should their primary indications be concomitant with gout, they may be good choices. Other drugs that lower serum urate include: ascorbic acid, calcitonin, estrogens, and aspirin (>3 g/day).

### Flare prophylaxis

When uric acid lowering therapy is started, it raises the possibility of acute gouty attack due to mobilization of uric acid from joint spaces and tissue to try to equilibrate.\textsuperscript{2,15} When the decision is made to begin chronic uric acid lowering therapy, consider adding prophylactic therapy as acute gout attacks occur in approximately 77% of patients.\textsuperscript{3} Colchicine is the most commonly recommended agent for this purpose, in doses of 0.6 mg to 2 times daily. NSAIDs may also be used in the lowest effective dose, also for 1 to 2 times daily. Duration of this therapy is typically 3 to 6 months, but may be longer, particularly if significant tophi are present.\textsuperscript{1,2,3,8,15}

### PATIENT EDUCATION

Patient education for the patient with gout centers around two topics: Lifestyle modifications and medication compliance.

Lifestyle modifications are equated with a “healthy lifestyle.” Exercise as appropriate for the individual and dietary modifications. The overall goal is a healthy BMI (18.5 to 24.9). Diet should be consistent with the current recommendations of a balance of protein, carbohydrate and fat. This will often serve more than one function as co-morbidities of diabetes mellitus, dyslipidemias and cardiovascular disease, among others, are often present. Gout-specific dietary changes would call for a reduction of purine-rich foods, primary meats and seafood, but although there are some vegetables high in purines, these seem to be less problematic. Also, zero to moderate alcohol intake is recommended, particularly beer and liquor.

Medication compliance may be a problem, particularly with allopurinol, but may apply to all chronic gout therapies.\textsuperscript{8,9} Studies have shown a compliance rate of approximately 18% to 25%. This is in part related to the occurrence of gout flares when initiating therapy, but these can be explained to patients and they need to be encourage to take the medication as directed, particularly when it is so long term.

### CONCLUSIONS

Gout is one of the oldest described diseases in human history with many afflicted. Fortunately, it is very treatable. The underlying pathology is an excess of uric acid due to errors of metabolism. Acute gouty attacks are managed as many acute pain situations, with the exception that a mainstay of therapy is colchicine, a very specific pain relief medication. Once the acute attack is controlled, a decision is made as to whether or not to initiate long term (sometimes lifelong) therapy to control uric acid production. Lifestyle modification, including some specific dietary changes can sometimes avoid the need for medication. If a medication is chosen, there are clear choices and fortunately some options.\textsuperscript{34}
### Acute Gout Therapy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Regimen(s) [PO unless noted]</th>
<th>Adverse Drug Reactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NONSTEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDs)</strong></td>
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<tr>
<td>Ibuprofen (eg, Advil, Motrin)</td>
<td>800 mg QID</td>
<td>GI bleeding/irritation, renal dysfunction</td>
<td>Cautions for GI bleeding/gastritis, other bleeding, renal dysfunction, fluid retention, hypertension, CHF, asthma, elderly. These are the most common NSAIDs, any in the class can be effective. Prophylactic Dosing: Lowest effective dose 1-2 times daily, 2-6 for weeks to months.</td>
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<tr>
<td>Indomethacin* (eg, Indocin)</td>
<td>25-50 mg QID for 3 days; then BID for 4-7 days.</td>
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<tr>
<td>Naproxen* (eg, Naprosyn)</td>
<td>500 mg BID for 3 days; then 250-500 mg QD for 4-7 days.</td>
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<tr>
<td>Sulindac* (eg, Clinoril)</td>
<td>200 mg BID for 7-10 days.</td>
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<td><strong>COLCHICINES</strong></td>
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<tr>
<td>Colchicine (Colcrys)</td>
<td>1.2 mg (2 tablets) at the first sign of a gout flare followed by 0.6 mg (1 tablet) one hour later.</td>
<td>Primary ADRs are GI (nausea/vomiting/diarrhea). Myopathy, neuropathy, dermatitis, alopecia. Severe overdose can result in myelosuppression, kidney and liver damage and CNS effects. Drug Interactions: CYP3A4 inhibitors (eg, macrolides, cyclosporine) ↑colchicine. The “low dose” approach is currently favored. Reduce dose in liver and renal dysfunction. Most effective within 24 hours of attack; ineffective &gt;48 hr. IV form not available but rarely used due to toxicity and deaths. Prophylactic Dosing: 0.6 mg 1-2 times daily in adults &gt;16 years of age. Max. dose 1.2 mg/day. Generally for 6 months.</td>
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<tr>
<td>[only approved product on the market]</td>
<td>0.5-0.6 mg Q hour until ADRs (usually N/V, diarrhea) or 6-8 mg. [ADRs 50-80%; rarely recommended]</td>
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<tr>
<td><strong>CORTICOSTEROIDS</strong></td>
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<tr>
<td>Prednisone (or equivalent)</td>
<td>40-60 mg QD for 3 days; decrease by 10-15 mg /day Q 3 days to discontinuation.</td>
<td>Avoid long term use. Hyperglycemia. Hypertension. Infections. GI bleeding. CNS disturbances.</td>
<td>Useful when NSAIDs are inappropriate. Preferred for polyarticular gout. Avoid long-term use. Caution in diabetes, hypertension, infections. Joint sepsis must be excluded. Intra-articular administration is an option and may be preferred over systemic, particularly for a single joint.</td>
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<tr>
<td>Methylprednisolone</td>
<td>100-150 mg QD for 1-2 days.</td>
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<tr>
<td>Triamcinolone acetonide</td>
<td>60 mg IM one dose</td>
<td>Intra-articular: Damage to structures. Joint infection.</td>
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<tr>
<td><strong>CORTICOTROPINS</strong></td>
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<tr>
<td>Corticotropin (eg, Acthar HP)</td>
<td>25 USP units SQ one dose for small joint involvement. 40 USP units IM or IV one dose, for large joint involvement or polyarticular attacks.</td>
<td>Avoid long term use. Hyperglycemia. Hypertension. Infections. CNS disturbances.</td>
<td>Repeat injections may be needed (Q 6-8 hours for 2-3 days). Requires intact pituitary-adrenal axis. Less effective if on long-term corticosteroids.</td>
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</tbody>
</table>

* FDA-labeled indication for treatment of gout.
Prophylaxis of Gout Attacks – Uric Acid Reduction

<table>
<thead>
<tr>
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<tr>
<td><strong>XANTHINE OXIDASE INHIBITORS</strong></td>
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<tr>
<td>Allopurinol (eg, Zyloprim)</td>
<td>100-800 mg daily; 300 mg daily most common. Avoid gout flares, dosage: 100 mg daily initially, increasing by 100 mg daily at 2-4 week intervals. Doses &gt;300 mg daily should be divided (2-3 times daily). Dosage adjustment needed for renal dysfunction (CrCl 10-20 mL/min ≤200 mg daily; CrCl &lt;10 mL/min ≤100 mg daily; CrCl &lt;3 mL/min, lengthen dosage interval).</td>
<td>Precipitation of gout attacks. Pruritus and rash common (2%). Severe hypersensitivity syndrome (0.4%; 20% mortality). Caution in renal dysfunction. Significant drug interactions: azathioprine, mercaptopurine, warfarin</td>
<td>Advantages: single daily dose up to 300 mg. Useful in overproducers and under-excretors. Effective in renal dysfunction.</td>
</tr>
<tr>
<td>Febuxostat (Uloric)</td>
<td>40-80 mg daily. No dose adjustment in mild/moderate renal or hepatic impairment.</td>
<td>Precipitation of gout attacks. Uncommon: Elevated serum transaminases, arthralgias, nausea, dizziness and rash. 10% of patients discontinue febuxostat. Drug interactions include: azathioprine, mercaptopurine, theophylline.</td>
<td>Indicated only when allopurinol is not appropriate. As or more effective than allopurinol, but not tested against allopurinol &gt;300 mg. Less hypersensitivity than allopurinol. Significantly more costly than allopurinol.</td>
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<td><strong>URICASES</strong></td>
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<td>Pegloticase (Krystexxa)</td>
<td>8 mg IV infusion (over no less than 120 min. via gravity feed, syringe-type pump, or infusion pump.) every 2 weeks. • Monitor serum uric acid levels before each infusion. • Pre-medicate with antihistamines and corticosteroids. • Administer only in a healthcare setting; be prepared to manage anaphylaxis.</td>
<td>Anaphylaxis. Infusion reactions (premedicate with antihistamines and corticosteroids). Gout flares, nausea/vomiting, contusion or ecchymosis, nasopharyngitis, constipation, chest pain. <strong>Contraindicated</strong> in Glucose-6-phosphate dehydrogenase (G6PD) Deficiency: Before therapy, patients at risk for G6PD deficiency (e.g., those of African and Mediterranean ancestry) should be screened due to the risk of hemolysis and methemoglobinemia.</td>
<td>Approved in September 2010. Indicated for treatment of chronic gout in adult patients refractory to conventional therapy. MOA: PEGylated uric acid-specific enzyme (urate oxidase) catalyzes oxidation of uric acid to allantoin (and excreted). Very expensive! 12/1/2010 - Savient Pharmaceuticals Inc announced that the drug's wholesale acquisition cost will be $2,300 per 8mg vial, or $59,800/yr (8mg dosed every 2 wks).</td>
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<td><strong>URICOSURICS</strong></td>
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To receive continuing education credit, please provide the following information:

1. Complete the participant information in the spaces provided. Use **BLUE** ink only.
2. Mail the completed form for scoring to the address listed below. The quiz must be postmarked by the expiration date. Faxed CE quizzes WILL NOT be accepted.

   **Mail to:** APA, 1211 Carmichael Way, Montgomery, AL  36106

3. CE processing is free for APA members. Non-members must include a processing fee of $20 per quiz.
4. No more than 3 quizzes will be accepted per month per individual.
5. Credit will be awarded for a passing grade of 80% or better. If you fail the exam, you may retake it once, and corrected answers must be in **RED** ink.
1. What is one of the common names of the ancient disease we call gout?
   a. Disease of Kings
   b. Disease of Queens
   c. Disease of Jacks
   d. Disease of the common people

2. The name 'gout' is derived from the Latin term 'gutta' which is translated to mean?
   a. Up
   b. Down
   c. Drop
   d. Joint

3. Podagra is a common presentation of gout and is defined as what?
   a. Multiple articular involvement
   b. Gout of the great toe
   c. The first attack of gout
   d. Gout of the thumb

4. How many people in the United States are estimated to suffer from gout?
   a. 4%
   b. 9%
   c. 13%
   d. 20%

5. What is the underlying metabolic disruption that predisposes to the development of gout?
   a. Hyperglycemia
   b. Hypolipidemia
   c. Hypouricemia
   d. Hyperuricemia

6. The laboratory definition hyperuricemia is what?
   a. ≥3.2 mg/dL
   b. ≥6.8 mg/dL
   c. ≥9.0 mg/dL
   d. ≥12.5 mg/dL

7. Uric acid is a normal byproduct of human metabolism. How much uric is produced by the average human in a day?
   a. <600 mg
   b. 600-800 mg
   c. 900-1000 mg
   d. >1100 mg

8. A tophus is a long term complication of gout. Which statement below best describes a tophus?
   a. A collection of tophi
   b. Chronic granulomatous deposition of monosodium urate crystals
   c. Another name for nephrolithiasis
   d. Calcium deposition along with hyperuricemia

9. Nephrolithiasis can be a long term complication of gout. Which of the following predisposes to the development of kidney damage?
   a. Overproducers
   b. Underexcretors
   c. Newly diagnosed patients with gout
   d. Patients taking colchicine

10. Which one of the following single items constitutes a definitive diagnosis for gout?
    a. Hyperuricemia
    b. Joint pain with swelling and redness
    c. Hard lumps in the ear lobe
    d. Monosodium urate crystals in synovial fluid

11. Which one of the following nonsteroidal anti-inflammatory agents (NSAIDs) does NOT have a specific labeled indication for treatment of gout pain?
    a. Ibuprofen
    b. Indomethacin
    c. Naproxen
    d. Sulindac

12. Which of the following colchicine dosage schedules represents the most current recommendations for treatment of acute gouty arthritis?
    a. 0.6 mg three times daily
    b. 1.2 mg three times daily
    c. 1.2 mg initially followed by 0.6 mg in one hour
    d. 0.6 mg initially followed by 1.2 mg in one hour

13. Which of the following is the oldest known therapy for acute gout?
    a. Indomethacin
    b. Prednisone
    c. Colchicine
    d. Garlic

14. In general and in the absence of specific indicating factors, what place in therapy is occupied by oral corticosteroids for acute gout, compared to NSAIDs and colchicine?
    a. First line
    b. Second line
    c. Third line
    d. Contraindicated

15. A rich diet has been classically associated with the development of gout. Proper diet and exercise is a common recommendation for many patients with many disorders. What is the “best” diet recommendation for gout among the choices below?
    a. A very low purine diet
    b. A high purine diet
    c. A diet in high fructose corn syrup
    d. A general “healthy” diet

16. Among the therapies available to lower uric acid levels in gout sufferers, which one of the following is generally considered the drug of choice?
    a. Allopurinol
    b. Febuxostat
    c. Colchicine
    d. Pegloticase

17. What is the maximum dose recommended for allopurinol in patients with gout?
    a. 100 mg/day
    b. 300 mg/day
    c. 500 mg/day
    d. 800 mg/day
18. A patient with gout has developed a rash while taking allopurinol. It is moderate in severity and very annoying; attempts to alleviate the rash have not been successful. What would be the next appropriate step in therapy?
a. Discontinue allopurinol and treat any gout flares with colchicine  
b. Discontinue allopurinol and initiate febuxostat  
c. Continue allopurinol and observe for rash resolution  
d. Discontinue allopurinol and begin pegloticase therapy

19. What is the mechanism of action of probenecid?
a. Block renal tubular reabsorption of uric acid to promote excretion  
b. Enhance the breakdown of uric acid to water soluble metabolites  
c. Block the metabolism of precursors to uric acid  
d. Prevents the inflammatory response in affected joints

20. There are other drugs generally prescribed for nongout indications that can have favorable effects for patients with gout. Which of the following drugs fall into this category?
a. Losartan  
b. Fenofibrate  
c. Aspirin in high doses  
d. All of the above

21. When uric acid lowering therapy is initiated in patients, it often precipitates acute gout attacks due to mobilization of uric acid deposits. Which of the following represents a standard regimen for flare prophylaxis?
a. Indomethacin 50 mg three times daily for 4 weeks  
b. Colchicine 0.6 mg twice daily for 6 months  
c. Colchicine 0.6 mg twice daily for 6 weeks  
d. Ibuprofen 800 mg four times daily for 6 months

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