Chapter 1: Gout and Hyperuricemia

INTRODUCTION

- *Gout* involves hyperuricemia, recurrent attacks of acute arthritis with monosodium urate (MSU) crystals in synovial fluid leukocytes, deposits of MSU crystals in tissues in and around joints (tophi), interstitial kidney disease, and uric acid nephrolithiasis.

ACUTE GOUTY ARTHRITIS: PATHOPHYSIOLOGY

- Uric acid is the end product of purine degradation. An increased urate pool in individuals with gout may result from overproduction or underexcretion.
- Purines originate from dietary purine, conversion of tissue nucleic acid to purine nucleotides, and de novo synthesis of purine bases.
- Overproduction of uric acid may result from abnormalities in enzyme systems that regulate purine metabolism (eg, increased activity of phosphoribosyl pyrophosphate [PRPP] synthetase or deficiency of hypoxanthine-guanine phosphoribosyl transferase [HGPRT]).
- Uric acid may also be overproduced because of increased breakdown of tissue nucleic acids, as with myeloproliferative and lymphoproliferative disorders. Cytotoxic drugs can result in overproduction of uric acid due to lysis and the breakdown of cellular matter.
- Dietary purines are insignificant in generating hyperuricemia without some derangement in purine metabolism or elimination.
- Two-thirds of uric acid produced daily is excreted in urine. The remainder is eliminated through gastrointestinal (GI) tract after degradation by colonic bacteria. Decline in urinary excretion to a concentration below the rate of production leads to hyperuricemia and an increased pool of sodium urate.
- Drugs that decrease renal uric acid clearance include diuretics, nicotinic acid, salicylates (<2 g/day), ethanol, pyrazinamide, levodopa, ethambutol, cyclosporine, and cytotoxic drugs.
- Deposition of urate crystals in synovial fluid results in inflammation, vasodilation, increased vascular permeability, complement activation, and chemotactic activity for polymorphonuclear leukocytes. Phagocytosis of urate crystals by leukocytes results in rapid lysis of cells and discharge of proteolytic enzymes into cytoplasm. The ensuing inflammatory reaction causes intense joint pain, erythema, warmth, and swelling.
- Uric acid nephrolithiasis occurs in ~10% of patients with gout. Predisposing factors include excessive urinary excretion of uric acid, acidic urine (pH <6), and highly concentrated urine.
- In acute uric acid nephropathy, acute kidney injury occurs because of blockage of urine flow from massive precipitation of uric acid crystals in collecting ducts and ureters. Chronic urate nephropathy is caused by long-term deposition of urate crystals in the renal parenchyma.
- Tophi (urate deposits) are uncommon and are a late complication of hyperuricemia. The most common sites are the base of the fingers, olecranon bursae, ulnar aspect of forearm, Achilles tendon, knees, wrists, and hands.

CLINICAL PRESENTATION

- Acute gout attacks are characterized by rapid onset of excruciating pain, swelling, and inflammation. The attack is typically monoarticular, most often affecting the first metatarsophalangeal joint (podagra), and then, in order of frequency, the insteps, ankles, heels, knees, wrists, fingers, and elbows. Attacks commonly begin at night, with the patient awakening with excruciating pain. Affected joints are erythematous, warm, and swollen.

Fever and leukocytosis are common. Untreated attacks last from 3 to 14 days before spontaneous recovery.

- Acute attacks may occur without provocation or be precipitated by stress, trauma, alcohol ingestion, infection, surgery, rapid lowering of serum uric acid by uric acid-lowering agents, and ingestion of drugs known to elevate serum uric acid concentrations.

DIAGNOSIS

- Definitive diagnosis requires aspiration of synovial fluid from the affected joint and identification of intracellular crystals of MSU monohydrate in synovial fluid leukocytes.
- When joint aspiration is not feasible, a presumptive diagnosis is based on presence of characteristic signs and symptoms as well as the response to treatment.

TREATMENT

- Goals of Treatment: Terminate the acute attack, prevent recurrent attacks, and prevent complications associated with chronic deposition of urate crystals in tissues.

Nonpharmacologic Therapy

- Local ice application is the most effective adjunctive treatment.
- Dietary supplements (eg, flaxseed, cherry, celery root) are not recommended.

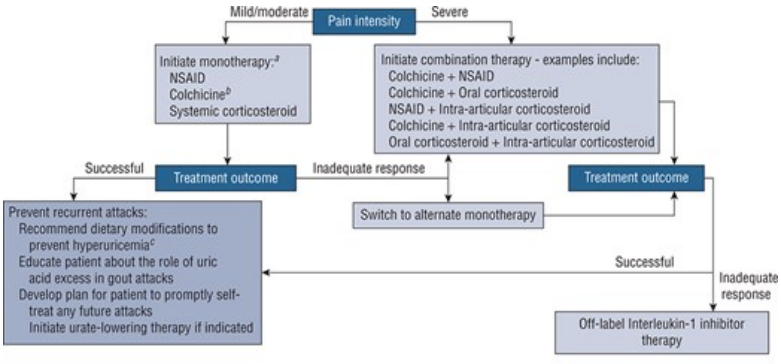
Pharmacologic Therapy (Fig. 1-1)

- Most patients are treated successfully with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine. Treatment should begin as soon as possible after the onset of an attack.

FIGURE 1-1

Algorithm for management of an acute gout attack.

(Algorithm derived from 2017 ACP, 2016 EULAR, and 2012 ACR gout guidelines.)



a) Recommendation for initial monotherapy with one of these medication groups supported unanimously by guidelines of the American College of Rheumatology (ACR), European League Against Rheumatism (EULAR), and American College of Physicians (ACP)
b) Colchicine should be started as soon as possible, ideally within 12-36 hours of pain onset
c) Noted as an area of inconclusive evidence by 2017 ACP guidelines

NSAIDS

- NSAIDs have excellent efficacy and minimal toxicity with short-term use. Indomethacin, naproxen, and sulindac have Food and Drug Administration (FDA) approval for gout, but others are likely to be effective (**Table 1-1**).

- Start therapy within 24 hours of attack onset and continue until complete resolution (usually 5–8 days). Tapering may be considered after resolution, especially if comorbidities such as impaired hepatic or kidney function make prolonged therapy undesirable.
- The most common adverse effects involve the GI tract (gastritis, bleeding, and perforation), kidneys (renal papillary necrosis, reduced glomerular filtration rate), cardiovascular system (increased blood pressure, sodium and fluid retention), and central nervous system (impaired cognitive function, headache, and dizziness).
- Selective cyclooxygenase-2 inhibitors (eg, celecoxib) may be an option for patients unable to take nonselective NSAIDs, but the risk-to-benefit ratio in acute gout is unclear, and cardiovascular risk must be considered.

TABLE 1-1

Dosage Regimens of Oral Nonsteroidal Anti-inflammatory Drugs for Treatment of Acute Gout

Generic Name	Initial Dose	Usual Range
Etodolac	300 mg twice daily	300–500 mg twice daily
Fenoprofen	400 mg three times daily	400–600 mg three to four times daily
Ibuprofen	400 mg three times daily	400–800 mg three to four times daily
Indomethacin	50 mg three times daily	50 mg three times daily initially until pain is tolerable then rapidly reduce to complete cessation
Ketoprofen	75 mg three times daily or 50 mg four times daily	50–75 mg three to four times daily
Naproxen	750 mg followed by 250 mg every 8 hours until the attack has subsided	—
Piroxicam	20 mg once daily or 10 mg twice daily	—
Sulindac	200 mg twice daily	150–200 mg twice daily for 7–10 days
Meloxicam	5 mg once daily	7.5–15 mg once daily
Celecoxib	800 mg followed by 400 mg on day one, then 400 mg twice daily for 1 week	—

Corticosteroids

- Corticosteroid efficacy is equivalent to NSAIDs; they can be used systemically or by intra-articular (IA) injection. If only one or two joints are involved, either IA or oral corticosteroids are recommended. Systemic therapy is necessary for polyarticular attacks.
- **Prednisone** or **prednisolone** oral dosing strategies include (1) 0.5 mg/kg daily for 5–10 days followed by abrupt discontinuation, or (2) 0.5 mg/kg daily for 2–5 days followed by tapering for 7–10 days. Tapering is often used to reduce the hypothetical risk of a rebound attack upon steroid withdrawal.
- **Methylprednisolone dose pack** is a 6-day regimen starting with 24 mg on day 1 and decreasing by 4 mg each day that may be considered.

- **Triamcinolone acetonide** 20–40 mg given by IA injection may be used if gout is limited to one or two joints; give 10–40 mg IA (large joints) or 5–20 mg IA (small joints). IA corticosteroids should be used with an oral NSAID, colchicine, or corticosteroid therapy.
- **Methylprednisolone** (a long-acting corticosteroid) given by a single intramuscular (IM) injection followed by a short course of oral corticosteroid therapy is another reasonable approach. Alternatively, IM corticosteroid monotherapy may be considered in patients with multiple affected joints who cannot take oral therapy.
- Short-term corticosteroid use is generally well tolerated. Use with caution in patients with diabetes, GI problems, bleeding disorders, cardiovascular disease, and psychiatric disorders. Avoid long-term use because of risk for osteoporosis, hypothalamic–pituitary–adrenal axis suppression, cataracts, and muscle deconditioning.
- **Adrenocorticotropic hormone (ACTH) gel:** 40–80 USP units IM every 6–8 hours for 2 or 3 days and then discontinued. Limit use to patients with contraindications to first-line therapies (eg, heart failure, chronic kidney disease, and history of GI bleeding) or patients unable to take oral medications. However, the high drug price excludes ACTH as a viable treatment option.

Colchicine

- **Colchicine** is highly effective in relieving acute gout attacks; when it is started within the first 24 hours of onset, about two-thirds of patients respond within hours. Use only within 36 hours of attack onset because the likelihood of success decreases substantially if treatment is delayed.
- Colchicine causes dose-dependent GI adverse effects (nausea, vomiting, and diarrhea). Non-GI effects include neutropenia and axonal neuromyopathy, which may be worsened in patients taking other myopathic drugs (eg, statins) or with impaired kidney function. Use colchicine with caution in patients taking P-glycoprotein or strong CYP450 3A4 inhibitors (eg, clarithromycin) due to increased plasma colchicine levels and potential toxicity; colchicine dose reductions may be required. Also use colchicine with caution in patients with impaired kidney or hepatic function.
- **Colcrys** is an FDA-approved colchicine product available in 0.6 mg oral tablets. The recommended dose is 1.2 mg (two tablets) initially, followed by 0.6 mg (one tablet) 1 hour later. Although not an FDA-approved regimen, the American College of Rheumatology (ACR) gout treatment guidelines suggest that colchicine 0.6 mg once or twice daily can be started 12 hours after the initial 1.2-mg dose and continued until the attack resolves. Colchicine is also available generically.

HYPERURICEMIA IN GOUT

- Recurrent gout attacks can be prevented by maintaining low uric acid levels, but adherence with nonpharmacologic and pharmacologic therapies is poor.

Nonpharmacologic Therapy

- Patient education should address the recurrent nature of gout and the objective of each lifestyle/dietary modification and medication.
- Promote weight loss through caloric restriction and exercise in all patients to enhance renal urate excretion.
- Alcohol restriction is important because consumption correlates with gout attacks. ACR guidelines recommend limiting alcohol use in all gout patients and avoidance of any alcohol during periods of frequent gout attacks and in patients with advanced gout under poor control.
- Dietary recommendations include limiting consumption of high-fructose corn syrup and purine-rich foods (organ meats and some seafood) and encouraging consumption of vegetables and low-fat dairy products. The DASH diet (Dietary Approaches to Stop Hypertension) may lower serum uric acid by ~1.0 mg/dL in hyperuricemic patients who are adherent. However, no studies have demonstrated that dietary intervention improves clinical outcomes such as reduction in gout flares.
- Evaluate the medication list for potentially unnecessary drugs that may elevate uric acid levels. The ACR guidelines recommend elimination of nonessential uric acid-elevating medications in patients with hyperuricemia when feasible (eg, thiazide and loop diuretics, calcineurin inhibitors, niacin). Low-dose aspirin for cardiovascular prevention should be continued because aspirin has a negligible effect on elevating serum uric acid.

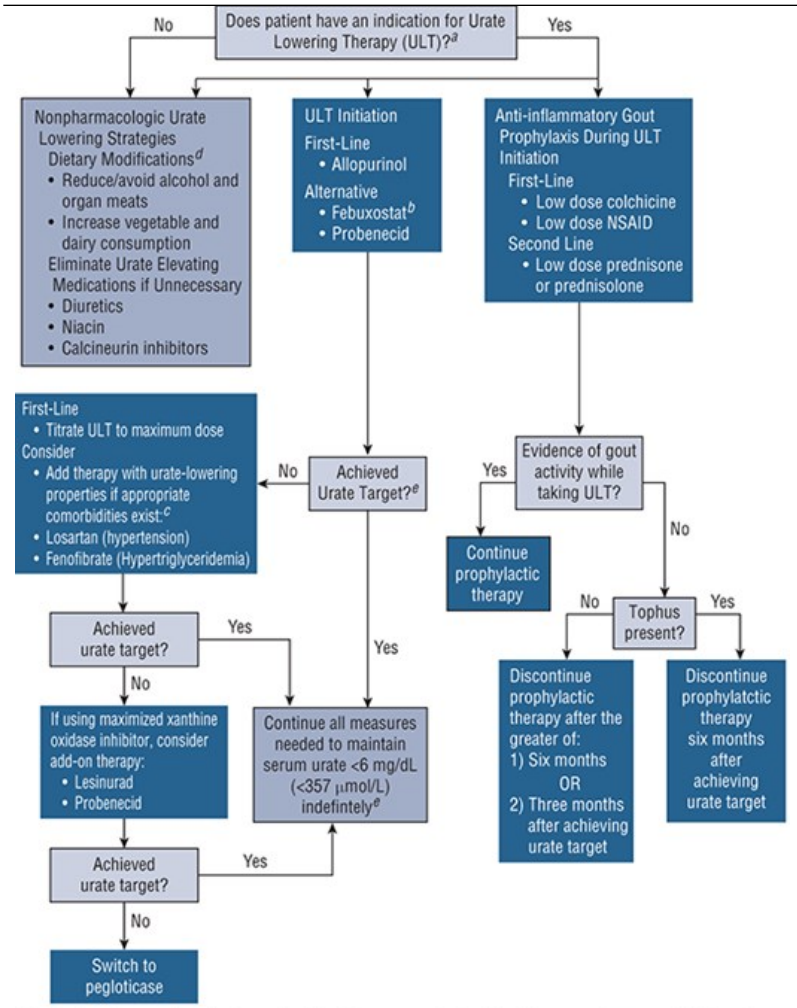
Pharmacologic Therapy (Fig. 1-2)

- After the first attack of acute gout, prophylactic pharmacotherapy is recommended if patients have two or more attacks per year, even if serum uric acid is normal or only minimally elevated. Other indications include presence of tophi, kidney disease, or history of uric acid urolithiasis.
- Urate-lowering therapy can be started during an acute attack if anti-inflammatory prophylaxis has been initiated.
- Apply a stepwise approach to hyperuricemia (**Fig. 1-2**). Xanthine oxidase inhibitors are recommended first-line therapy, with uricosurics reserved for patients with a contraindication or intolerance to xanthine oxidase inhibitors. In refractory cases, combination therapy with a xanthine oxidase inhibitor plus a drug with uricosuric properties (probenecid, losartan, or fenofibrate) is suggested. Pegloticase may be used in severe cases in which the patient cannot tolerate or is not responding to other therapies.
- The ACR guideline goal of urate-lowering therapy is to achieve and maintain serum uric acid <6 mg/dL (357 µmol/L), and preferably <5 mg/dL (297 µmol/L) if gout is severe or signs and symptoms of gout persist. Urate lowering should be prescribed for long-term use.

FIGURE 1-2

Algorithm for management of hyperuricemia in gout.

NSAID, nonsteroidal anti-inflammatory drug; ULT, urate-lowering therapy; XOI, xanthine oxidase inhibitor. (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

Xanthine Oxidase Inhibitors

- Xanthine oxidase inhibitors reduce uric acid by impairing conversion of hypoxanthine to xanthine and xanthine to uric acid. Because they are effective in both overproducers and underexcretors of uric acid, they are the most widely prescribed agents for long-term prevention of recurrent gout attacks.

- **Allopurinol** lowers uric acid levels in a dose-dependent manner. ACR guidelines recommend a starting dose no greater than 100 mg daily in patients with normal kidney function and no more than 50 mg/day in patients with chronic kidney disease (stage 4 or worse) to avoid allopurinol hypersensitivity syndrome and prevent acute gout attacks common during initiation of urate-lowering therapy. The dose should be titrated gradually every 2–5 weeks up to a maximum of 800 mg/day until the serum urate target is achieved.

- Mild adverse effects of allopurinol include skin rash, leukopenia, GI problems, headache, and urticaria. 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, occurs rarely but is associated with a 20%–25% mortality rate.

- **Febuxostat** (Uloric) also lowers serum uric acid in a dose-dependent manner. The recommended starting dose is 40 mg once daily. Increase the dose to 80 mg once daily for patients who do not achieve target serum uric acid concentrations after 2 weeks of therapy. Adverse events include nausea, arthralgias, and minor hepatic transaminase elevations. Febuxostat does not require dose adjustment in hepatic or kidney dysfunction. Recent clinical trial evidence demonstrated an increase in all-cause and cardiovascular mortality compared to allopurinol, resulting in addition of a warning in the FDA-approved labeling. Because of these safety concerns, lack of evidence of superior efficacy compared to equivalent-dosed allopurinol, and increased cost, febuxostat is considered a second-line option. Due to rapid mobilization of urate deposits during initiation, give concomitant therapy with colchicine or an NSAID for at least the first 8 weeks of therapy to prevent acute gout flares.

Uricosurics

- Uricosuric drugs increase renal clearance of uric acid by inhibiting the postsecretory renal proximal tubular reabsorption of uric acid. Patients with a history of urolithiasis should not receive uricosurics. Start uricosuric therapy at a low dose to avoid marked uricosuria and possible stone formation. Maintaining adequate urine flow and urine alkalinization during the first several days of therapy may also decrease likelihood of uric acid stone formation. Uricosuric treatment is limited to patients with creatinine clearance (CrCl) >45–50 mL/min.

- **Probenecid:** The initial dose is 250 mg twice daily for 1–2 weeks, then 500 mg twice daily for 2 weeks. Increase the daily dose thereafter by 500-mg increments every 1–2 weeks until satisfactory control is achieved or a maximum dose of 2 g/day is reached. Major side effects include GI irritation, rash and hypersensitivity, precipitation of acute gouty arthritis, and urolithiasis.

- **Lesinurad** (Zurampic) inhibits urate transporter 1 in proximal renal tubules, thereby increasing uric acid excretion. It 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 uric acid concentrations with xanthine oxidase inhibitor monotherapy. The approved lesinurad dose is 200 mg once daily in the morning with food and water in combination with a xanthine oxidase inhibitor. Lesinurad should not be used in patients with CrCl <45 mL/min. Adverse effects include urticaria and elevated levels of serum creatinine, lipase, and creatine kinase. It carries a black box warning about increased risk of acute renal failure when used in the absence of xanthine oxidase inhibitor therapy. A combination product (Duzallo) is available that contains two different allopurinol strengths: lesinurad 200 mg/allopurinol 200 mg (for patients with CrCl 45–59 mL/min) and lesinurad 200 mg/allopurinol 300 mg (for patients with CrCl >59 mL/min).

Pegloticase

- **Pegloticase** (Krystexxa) is a pegylated recombinant uricase that reduces serum uric acid by converting uric acid to allantoin, which is water soluble. Pegloticase is indicated for antihyperuricemic therapy in adults refractory to conventional therapy.

- The dose is 8 mg by IV infusion over at least 2 hours every 2 weeks. Because of potential infusion-related allergic reactions, patients must be pretreated with antihistamines and corticosteroids. Pegloticase is substantially more expensive than first-line urate-lowering therapies.

- The ideal duration of pegloticase therapy is unknown. Development of pegloticase antibodies resulting in loss of efficacy may limit the duration of effective therapy.

- Because of its limitations, reserve pegloticase for patients with refractory gout who are unable to take or have failed all other urate-lowering therapies.

Miscellaneous Urate-Lowering Agents

- **Fenofibrate** is thought to increase clearance of hypoxanthine and xanthine, leading to a sustained reduction in serum urate concentrations of 20%–30%.

- **Atorvastatin** and **rosuvastatin** have also been associated with serum uric acid lowering, although the effect is less than with fenofibrate. The mechanism is unclear but is thought to be due to decreased renal reabsorption of uric acid.

- **Losartan** inhibits renal tubular reabsorption of uric acid and increases urinary excretion, properties that are not shared with other angiotensin II

receptor blockers. It also alkalinizes the urine, which helps reduce the risk for stone formation.

- **Amlodipine**, **nifedipine**, and **diltiazem** (calcium channel blockers) have been associated with a lower risk of gout, which has been attributed to increased renal elimination of uric acid.

Anti-Inflammatory Prophylaxis During Initiation of Urate-Lowering Therapy

- Initiation of urate-lowering therapy can precipitate an acute gout attack due to remodeling of urate crystal deposits in joints after rapid lowering of urate concentrations. Prophylactic anti-inflammatory therapy is often used to prevent such gout attacks.
- The ACR guidelines recommend low-dose oral colchicine (0.6 mg twice daily) or low-dose NSAIDs (eg, naproxen 250 mg twice daily) as first-line prophylactic therapies, with stronger evidence supporting use of colchicine. For patients on long-term NSAID prophylaxis, a proton pump inhibitor or other acid-suppressing therapy is indicated to protect from NSAID-induced gastric problems.
- Low-dose corticosteroid therapy (eg, prednisone ≤10 mg/day) is an alternative for patients with intolerance, contraindication, or lack of response to first-line therapy. The potential severe adverse effects of prolonged corticosteroid therapy preclude their use as first-line therapy.
- Continue prophylaxis for at least 6 months or 3 months after achieving target serum uric acid, whichever is longer. For patients with one or more tophi, continue prophylactic therapy for 6 months after achieving the serum urate target (**Fig. 1-2**).

EVALUATION OF THERAPEUTIC OUTCOMES

- Check the serum uric acid level in patients suspected of having an acute gout attack, particularly if it is not the first attack, and a decision is to be made about starting prophylaxis. However, acute gout can occur with normal serum uric acid concentrations.
- Monitor patients with acute gout for symptomatic relief of joint pain as well as potential adverse effects and drug interactions related to drug therapy. Acute pain of an initial gout attack should begin to ease within about 8 hours of treatment initiation. Complete resolution of pain, erythema, and inflammation usually occurs within 48–72 hours.
- For patients receiving urate-lowering therapy, obtain baseline assessment of kidney function, hepatic enzymes, complete blood count, and electrolytes. Recheck the tests every 6–12 months in patients receiving long-term treatment.
- During titration of urate-lowering therapy, monitor serum uric acid every 2–5 weeks; after the urate target is achieved, monitor uric acid every 6 months.
- Because of the high rates of comorbidities associated with gout (diabetes, chronic kidney disease, hypertension, obesity, myocardial infarction, heart failure, and stroke), elevated serum uric acid concentrations or gout should prompt evaluation for cardiovascular disease and the need for appropriate risk reduction measures. Clinicians should also look for possible correctable causes of hyperuricemia (eg, medications, obesity, malignancy, and alcohol abuse).

See Chapter 109, Gout and Hyperuricemia, authored by Michelle A. Fravel and Michael E. Ernst, for a more detailed discussion of this topic.