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Acute Gout Flare Associated with Healthy Lifestyle Modification: A Case and Review

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Gout affects at least 8 million people in the United States alone. This number is on the rise around the world. Dietary and healthy lifestyle modifications are recommended in order to reduce risk of gout, as well as other diseases including hyperlipidemia, obesity and hypertension. Below is a case of acute gout in a young healthy patient whom recently underwent a dietary change to assist with weight loss. In addition, the most recent recommendations of the American College of Rheumatology for treatment of acute gout flares are summarized.

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INTRODUCTION:

Gout was first documented in 2600 BC, when the Egyptians described it as an arthritis affecting the great toe (1). This arthropathy is characterized by intraarticular uric acid deposition in the form of monosodium urate crystals (MSU) secondary to hyperuricemia and is seen in the great toe up to 50% of the time on initial presentation (2). Leeuwenhoek provided the first description of uric acid crystals under a microscope, while Garrob proposed the mechanism of hyperuricemia, monosodium urate (MSU) crystal deposition and gout in the mid 19th century (3). In 1961, McCarty and Hollander visualized MSU crystals under a polarizing light microscope. This visualization technique is still used today as the gold standard for rapid and definitive diagnosis of the disease (2).

PATHOPHYSIOLOGY:

Uric acid levels are low in pre-pubescent children. When males hit puberty, a rise in uric acid is seen, with levels reaching 5-6 mg/dL. Uric acid levels normally remain within this range and do not increase with age (5). Premenopausal females have less of a predisposition for gouty arthritis due to their high levels of estrogen. Estrogen allows

larger amounts of UA to be excreted through the urine. After menopause, UA begins to reach levels of around 5-6 mg/dL, equivalent to what is seen in males. This drop in estrogen explains why females whom are affected by gout tend to be of advanced age (7).

Normal levels of uric acid in the adult population are gender dependent, with the upper limits of normal considered to be 5-6 mg/dL (8). Hyperuricemia, however, is defined as levels greater than 7 mg/dL (9).

Uric acid is the final byproduct of purine metabolism via the enzyme xanthine oxidase in the liver. In lesser-evolved mammals, uric acid is further metabolized to allontoin by the enzyme uricase. Humans and other high-level mammals lack this enzyme. The evolutionary benefit of this deficit is that uric acid serves as a potent antioxidant and is one of the few antioxidants humans can self-synthesize. Once uric acid is circulated through the blood, it can then excreted by the kidneys (10).

Up to 90% of hyperuricemia is due to a deficiency in uric acid secretion (11). Lack of proper kidney excretion leads to excess uric acid in the blood stream, creating a gradient high enough to force the kidneys to filter out uric acid (10). The remaining 10% of the population develops hyperuricemia due to the over production of uric acid (11). Acute gouty flares are often triggered by extracellular fluid (ECF) balance disturbances leading to MSU deposition. Certain situations and pharmaceutical drugs can cause changes in ECF, including trauma, surgery, starvation, dehydration, fatty foods, high meat and/or fish consumption, diuretics, allopurinol and low dose aspirin (4).

Long standing hyperuricemia may lead to the asymptomatic deposition of uric acid crystals in synovial fluid. Gouty flares are typically a result of and directly proportional to the degree of MSU supersaturation (12). Higher levels of uric acid in the blood can cause crystal deposition, but there is no correlation between the level of hyperuricemia and the severity of a gouty attack (13). Although the level of hyperuricemia does not affect the severity of gout, other features of the MSU crystals do. A study by Fiddis et al. showed that characteristics of the crystals such as size charge, origin, nucleation and proteins coating the crystals can cause varying degrees of inflammation related to crystal deposition (14).

After crystal deposition has occurred, neutrophils direct the inflammatory response. Neutrophils play a central role in the amplification of gouty inflammation. Neutrophils and neutrophils containing MSU cystals are over abundant in synovial fluid analysis, making their appearance upon microscopic examination the hallmark of an acute gout (15). The interaction of neutrophils with MSU crystals leads to further inflammatory mediators being released (16). One such mediator is interleukin-1 (IL-1) beta. Interlukin-1 beta is a key inflammatory mediator and has been shown to play a primary role in the inflammatory response of animal models that lack IL-1 receptors (17).

ACUTE GOUT PRESENTATION & WORK-UP:

Signs and symptoms of an acute gout attack consist of severe pain in one or more joints with swelling, redness, warmth and disability. Up to 80% of acute attacks occur in a single joint. The most commonly affected joint is the first metatarsophalangeal joint, termed podagra when it occurs here. The onset is sudden, usually within a 24-hour period and with symptoms peaking between 12-24 hours after onset (9). Complete resolution often occurs with or without treatment and within a few days of the onset of the attack (4).

Work up of a patient with undiagnosed gout should include arthrocentesis with cell count, culture, gram stain and examination under polarizing light microscope. Intra- and extra-cellular MSU crystals that are negatively birefringent should be seen on microscopic examination. This method is 85% sensitive and 100% specific for an acute gout attack (18). Uric acid blood

levels are not necessary as they could be high, normal, or low during an acute flare (19).

Recent studies have shown ultrasound imaging to be useful in the diagnosis of acute gouty flares. Ultrasound is diagnostic of gout when hyperehcoic, linear densities are appreciated overlying the surface of joint cartilage, with sensitivity and specificity of 44% and 99% respectively (20).

CLINICAL CASE:

A healthy 34-year-old male with benign history presented with a chief complaint of a painful, swollen, fourth toe. He relates the toe became painful while at work during the night shift. He denies history of trauma. He admits to pain to palpation and rates his pain a 5/10. Physical examination revealed a 4th digit that was edematous and mildly erythematous. A heloma molle was noted to the lateral aspect of the 4th digit that was painful to touch. At this time, devitalized tissues to the 4th digit were debrided. A toe spacer was dispensed between the 4th and 5th digits. Patient was instructed on homecare with follow-up in 3 weeks.

The next day, the patient returned to the office with increased pain, swelling and redness to the 4th digit. The level of pain continued to intensify through the night and into the morning. He now rates his pain a 10/10 on the pain scale. He made claims that the digit was exquisitely painful, even to the lightest of touches. He again denied any trauma or previous injury to the digit. He also denied any recent open wounds to the lower extremity. He had no history of gouty arthritis or other arthropathies. Further questioning about the patient's diet revealed he had undergone a recent dietary change, known as the "Paleo diet". Along with the dietary change, he reported an increase his activity level. He is now partaking in an exercise regimen known as Crossfit.

On physical exam the 4th digit is erythematous and edematous with no open wounds or drainage present. There is no streaking, erythema or swelling proximal to the 4th digit. His neurovascular status is intact. No plain films or further workup were deemed necessary.

Patient was assessed and thought to be having an acute gout flare. He was instructed on proper gouty diet protocol and adequate hydration. He was prescribed oral colchicine and instructed to follow up in 1 week. The patient called back days later to cancel his follow up claiming that redness, swelling and pain had resolved. The flare was assumed to be secondary to his dietary change, which includes an increase in the amount of meat as a percentage of his caloric intake.

PALEO DIET:

The Paleolithic diet has recently gained popularity throughout the United States. Endorsers of paleo believe that this diet is most similar to what was used by our ancestors over the last 2 million years. They claim that populations of people exhibit bills of excellent health, not complicated by many of the epidemics we see today, because of the paleo lifestyle. These 84 tribes are the last remaining hunters and gatherers in the world. Advocates for paleo attribute their superior health to a reliance on the hunter-gatherer lifestyle they continue to utilize.

The diet is based on the belief that the genetic code of our bodies has not yet adapted to properly digest the foods we eat today, such as refined sugars and salts. Key features of the paleolithic diet are the high consumption of vegetables, fruits and meat, combined with a moderate consumption of nuts and berries, and a low consumption of grains. In addition, those on the paleo diet consume no milk or dairy products, legumes, refined carbohydrates, refined salt, or alcohol (Cordain et al., 2000, 2002/M. Osterdahl European journal of clinical nutrition). The latter are eliminated because these foods did not become staples until long after the Paleolithic era and the appearance of modern hominids (Jonsson et al/Cardiovascular Diabetology). The diet also emphasizes a higher potassium intake, increased omega 3

fatty acids and mono-unsaturated fats, and decreased trans-saturated fats.

Those following the paleo diet obtain approximately 30% of their daily calories from protein. This is a large increase over the typical western diet, which revolves around a 15% caloric intake from protein. Non-starchy fruits and vegetables will compromise about 40% of caloric intake.

One specific culture that has adopted this dietary style is the Crossfit community. This style of exercise incorporates aspects of cardiovascular activity with Olympic style weightlifting and gymnastics into a high intensity, maximal effort workout. Workouts are often done in large classes, leading to a community-like feel. Friendly competition and high performance are two of the sports more appealing aspects.

High-level athletes competing in this sport are always looking for an edge and many turn toward nutrition. The paleolithic diet has been widely accepted in this community for this exact reason. With athletes looking to increase energy levels, build lean muscle mass, lose unnecessary weight in the form of fat reserves and recover faster, they have turned to the paleo diet. A recent study in the European Journal of Clinical Nutrition showed that the paleo diet improved lipid profiles and lowered blood glucose levels in type II diabetic patients (21,22)

TREATMENT:

In 2013, the American College of Rheumatology published a 2-part article on the medical and pharmacological management of gouty arthritis. For acute gouty attacks, the college reviewed current pharmacologic treatment options. Those recommendations will be summarized in the paragraphs to follow. Recommendation levels are graded A-C as described in table 1.

The ACR provided a level C recommendation for initiating pharmacologic therapy and treatment within 24 hours of the onset of a gouty arthritis flare. These recommendations were based on a consensus from the investigation panel that better patient outcomes result from timely pharmacologic intervention during initial symptoms. The panel gave a level B recommendation for patient education on the signs and symptoms of acute gouty flares in order for patients to initiate treatment without consultation of their doctors.

Pharmacologic treatments of acute gout flares include oral colchicine, NSAIDs, oral corticosteroids or intraarticular corticosteroid injections. The panel gave levels of recommendations on each treatment and subjectively created scenarios for which treatments are appropriate. The scenarios were based on the widely accepted VAS score, number of joints involved, size of joints involved, patient's history of gouty flares and current pharmacologic management of uric acid.

The treatment algorithm for an acute gouty flare begins with patient's initial pain rating. There is a level A recommendation for treatment of mild to moderate pain of 1 joint, a few small joints or 1-2 large joints with monotherapy (figure1). The next recommendation is for reassessment of pain within 24 hours. If the pain does not decrease within 24 hours by >20% or if at 24 hours there is not a 50% reduction in pain, the panel gives level C recommendation for the addition of a 2nd pharmacologic agent or changing monotherapy.

Initiating monotherapy with indomethacin, naproxen, sulindac or celecoxib were all given a level A recommendation. Dosing for indomethacin and naproxen should be the maximum recommended by FDA until the course of the acute attack resolves (A level recommendation). Sulindac was given a level B recommendation at maximum dose. Lastly, the Cox 2 selective celoxicib was given a B level recommendation. Dosing is recommended at 800 mg initially, followed by 400 mg later in the day, and then 400 mg once daily until an attack resolves. This recommendation is made with the warning that due to the need for maximum dosing with this medication, the

long-term risks and benefits profile has not yet been determined.

Monotherapy with colchicine was given an A level recommendation. Colcihcine, however, has complex recommendations and lower levels of evidence of dosing than NSAID therapy. The panel gave a C level recommendation for initiation within 36 hours of the onset of symptoms. Dosing at 1.2 mg initially, followed by 0.6 mg 1 hour later, and then 0.6 mg q12h until flair resolves was given level B recommendation. The complication with administering this medication occurs if the patient is already taking colchicine. If the patient has had prophylactic colchicine within the last 14 days, consider adding a second initial treatment therapy.

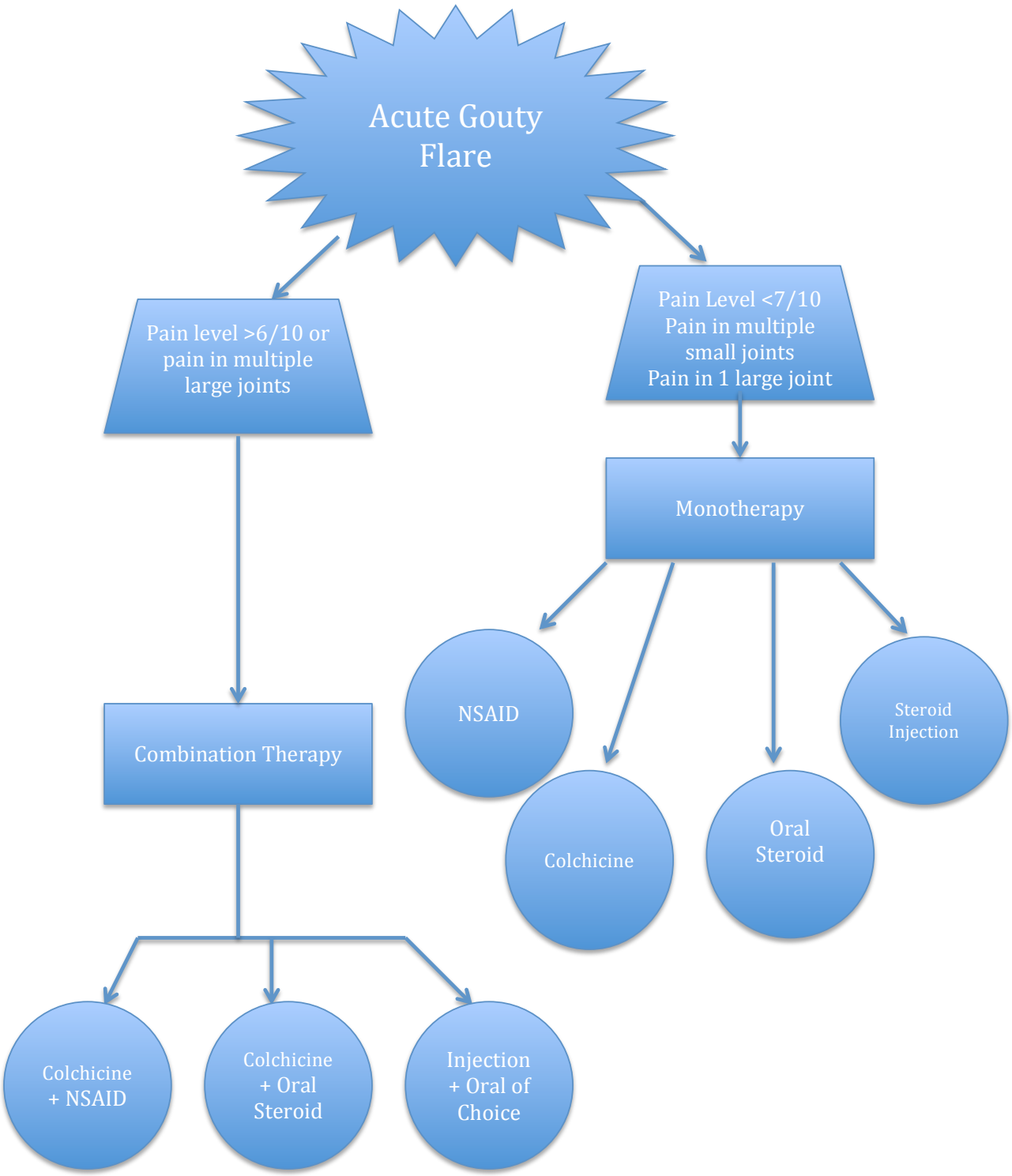
Initiation of treatment with oral prednisone has a grade A level recommendation from the panel. The dosing for initiation of this monotherapy is 0.5 mg/kg for 5-10 days, also given an A level recommendation. They do not recommend tapering; rather abruptly discontinue to the oral prednisone. Interestingly, the popular Medrol dose pack was only given a C level recommendation. Intra-articular steroid injection was given level B evidence with concentration and steroid type varying based on joint size.

For VAS scores of 7/10 or greater, large polyarticular attacks, or non-responsive patients, the committee made a level C recommendation for combination therapy. The following combinations are acceptable: 1. Colchicine + aforementioned NSAID 2. Colchicine+ oral steroid 3. Injectable Steroid + any oral treatment including systemic corticosteroids.

Table 1. Dosing Guidelines for Oral Medications in Acute Gout Flares (23)

Oral Treatment	**Dosing**	**Treatment Time Frame**
Colchicine (Level B)	1.2 mg then 0.6 mg 1 hour later followed by 0.6 mg q12h there after	Begin treatment w/in 36 hours of onset and continue until flare resolves
Indomethacin (Level A)	50 mg tid to qid maximum dose of 200 mg qd	Shortest time possible; until resolution occurs
Naproxen (Level A)	750 mg initially followed by 500 mg bid	Shortest time possible; until resolution occurs
Celoxicib (Level B)	800 mg initial dose followed by 400 mg later in day and 400 mg daily there after	Shortest time possible; until resolution occurs
Oral Prednisone (level A)	0.5 mg/kg per day	5-10 days with no tapering required

Figure 1. Algorithm for treatment of acute gout flare. Adapted from (23).



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