Clinical Policy Bulletin:  
Gout

Number: 0810

Policy

Aetna considers the following tests medically necessary for the diagnosis of gout:

- Measurement of blood uric acid levels
- Measurement of erythrocyte sedimentation rate
- Polarized light microscopy for identification of crystal in synovial fluids obtained from joints or bursas (as well as material aspirated from tophaceous deposits, if any)
- Magnetic resonance imaging for gouty tophus, which may mimic an infectious or neoplastic process.

Aetna considers the following tests for the diagnosis of gout experimental and investigational because their value in diagnosing gout has not been established:

- Measurement of 24-hour urine uric acid levels
- Measurement of blood lead levels
- Measurement of salivary uric acid levels
- Measurement of scalp hair uric acid levels

Aetna considers pegloticase (Krystexxa) medically necessary for the treatment of persons with symptomatic gout when all of the following criteria are met:

- At least 3 gout flares in the previous 18 months that were inadequately controlled by colchicine and non-steroidal anti-inflammatory drugs, or at least 1 gout tophus or gouty arthritis;
- Failure to normalize serum uric acid to less than 6 mg/dL after 3 months of maximum medically appropriate dose of xanthine oxidase inhibitors (maximum recommended dosages of allopurinol [Zyloprim] and febuxostat [Uloric] are 800 mg/day and 80 mg/day, respectively), or when xanthine oxidase inhibitors are contraindicated;
- Member has undertaken appropriate life style modifications, i.e. limiting of alcohol consumption and other medications known to precipitate gout attacks have been discontinued/changed when possible;
Member does not have G6PD deficiency. (Persons at higher risk for G6PD deficiency (e.g., those of African and Mediterranean ancestry) should be screened due to the risk of hemolysis and methemoglobinemia. G6PD deficiency is a contraindication for Krystexxa therapy).

Aetna considers interleukin-1 inhibitors (e.g., use of anakinra, canakinumab and rilonacept) experimental and investigational for the treatment of gout because their effectiveness for this indication has not been established.

See also CPB 0300 - Hair Analysis, CPB 0595 - Kineret (Anakinra), and CPB 0770 - Rilonacept (Arcalyst).

Background

Gout is a condition caused by the over-production or under-excretion of uric acid, resulting in the deposition of monosodium urate crystals in the joints or soft tissue. The disease is often, but not always, associated with increased blood uric acid levels. The four phases of gout are (i) asymptomatic hyperuricemia, (ii) acute gouty arthritis, (iii) inter-critical gout, and (iv) chronic tophaceous gout. The peak incidence of gout occurs in patients 30 to 50 years old, and the condition is much more common in men than in women. Individuals with asymptomatic hyperuricemia do not require specific treatment; however, attempts should be made to decrease their urate levels by encouraging them to make dietary and lifestyle modifications (e.g., a low carbohydrate, high protein and unsaturated fat diet). Acute gout most commonly affects the first metatarsal joint of the foot, but the small joints of the hands, wrists and elbows may also be involved. Gout rarely occurs in the shoulders, hips, sacroiliac joints or spine. Gout in the elderly differs from classical gout found in middle-aged men in several respects: it has a more equal gender distribution, frequent polyarticular presentation with involvement of the joints of the upper extremities, fewer acute gouty episodes, a more indolent chronic clinical course, and an increased incidence of tophi, which are deposits of monosodium urate crystals in people with longstanding high levels of uric acid in the blood and are commonly seen in conjunction with gout. Long-term diuretic use in patients with hypertension or congestive cardiac failure, renal insufficiency, prophylactic low-dose aspirin, and alcohol abuse (particularly by men) are factors associated with the development of hyperuricemia and gout in the elderly (Pittman and Bross, 1999; Harris et al, 1999; Agudelo and Wise, 2000; Agudelo and Wise, 2001).

Segal and Albert (1999) stated that diagnosis of the crystal-induced arthritides is primarily based on microscopic identification of crystals in synovial fluid. Harris and colleagues (1999) noted that definitive diagnosis requires joint aspiration with demonstration of birefringent crystals in the synovial fluid under a polarized light microscope.

While blood level of uric acid has been commonly used as a diagnostic indicator of hyperuricemia and gout, the value of salivary level, scalp hair level, as well as 24-hour urine level of uric acid in diagnosing gout has not been established. Microscopic analysis by means of compensated polarized light and culture of synovial fluid helps differentiate gouty arthritis from other arthropathies, and the presence of monosodium urate crystals establishes the diagnosis of gout. When gout is suspected, yet the initial examination
does not reveal the telltale crystals, re-examination of synovial fluid is warranted. It is important to note that diagnosis of gout does not rule out the possibility of concurrent arthritic conditions (Uy et al, 1996; Owen-Smith et al, 1998; Kobayashi et al, 1998; Pittman and Bross, 1999; Schlesinger et al, 1999).

Report of a task force of the Standing Committee for International Clinical Studies Including Therapeutics on the diagnosis of gout (Zhang et al, 2006a) stated that radiographs have little role in diagnosis, though in late or severe gout radiographical changes of asymmetrical swelling and subcortical cysts without erosion may be useful to differentiate chronic gout from other joint conditions.

Treatment goals include termination of the acute attack, prevention of recurrent attacks and prevention of complications associated with the deposition of urate crystals in tissues. Pharmacotherapy remains the mainstay of treatment. Acute attacks may be terminated with the use of non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or intra-articular injections of corticosteroids. Probenecid, sulfinpyrazone and allopurinol can be used to prevent recurrent attacks. In patients with peptic ulcer disease, selective cyclo-oxygenase-2 (COX-2) inhibitors provide another treatment option. In the presence of renal impairment, allopurinol is the treatment of choice for urate-lowering therapy, but doses of allopurinol and colchicine must be adjusted. Urate-lowering therapy should only be used if recurrent episodes of gout occur despite aggressive attempts to reverse or control the underlying causes. It should not be introduced or discontinued during an acute episode of gout. Obesity, alcohol consumption and certain foods and medications can contribute to hyperuricemia. These risk factors should be identified and modified (Pittman and Bross, 1999; McGill, 2000; van Doornum and Ryan, 2000; Zhang et al, 2006b).

Caution should be exercised when prescribing NSAIDs for the treatment of acute gouty arthritis in the elderly. Short-acting NSAIDs (e.g., diclofenac and ketoprofen) are preferred, but these drugs are not recommended in patients with peptic ulcer disease, renal failure, uncontrolled hypertension or cardiac failure. Colchicine is poorly tolerated in the elderly and is best avoided. Intra-articular and systemic corticosteroids are increasingly being used for treating acute gouty flares in elderly patients with medical disorders contraindicating NSAID therapy. Urate-lowering drugs are poorly tolerated and the frequent presence of renal impairment in the elderly renders these drugs ineffective. Allopurinol is the urate-lowering drug of choice, but its use in the elderly is associated with an increased incidence of both cutaneous and severe hypersensitivity reactions. To minimize this risk, the dosage of allopurinol must be kept low (Fam, 1998).

Cronstein and Terkeltaub (2006) stated that despite the detailed mechanistic picture for gouty inflammation, there are no placebo-controlled, randomized clinical studies for any of the therapies commonly used, although comparative studies have demonstrated that many NSAIDs are equivalent to indomethacin with respect to controlling acute gouty attacks. In general, the 1st-line of anti-inflammatory therapy for acute gout is NSAIDs, and the selective COX-2 inhibitor, celecoxib, can be used where appropriate. The 2nd-line of treatment is glucocorticoids, given systemically (intramuscular, intravenous, or oral) or intra-articularly. Alternatively, synthetic adrenocorticotropic hormone is effective, partly via induction of adrenal glucocorticosteroids and partly via rapid peripheral suppression of leukocyte activation by melatonin receptor 3 signaling. The 3rd-line of treatment is oral colchicine, which is highly effective when given early in an acute gouty attack, but it is poorly tolerated because of predictable gastrointestinal side effects.
The task force of the Standing Committee for International Clinical Studies Including Therapeutics on the management of gout (Zhang et al, 2006b) noted that recommended drugs for acute gout attacks were oral NSAIDs, oral colchicine, or joint aspiration and injection of corticosteroid. Urate-lowering therapy is indicated in patients with recurrent acute attacks, arthropathy, tophi, or radiographical changes of gout. Allopurinol was confirmed as effective long-term urate-lowering therapy. If allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, allopurinol de-sensitization, or a uricosuric. The uricosuric benzbromarone is more effective than allopurinol and can be used in patients with mild-to-moderate renal insufficiency but may be hepatotoxic. When gout is associated with the use of diuretics, the diuretic should be stopped if possible. For prophylaxis against acute attacks, either colchicine 0.5 to 1 mg daily or an NSAID (with gastro-protection if indicated) is recommended.

The clinical guideline on the management of initial gout in adults by the University of Texas at Austin (2009) included pharmacotherapies (e.g., colchicine, corticosteroids [intra-articular or systemic], NSAIDs, and vitamin C), as well as non-pharmacological management (e.g., avoidance of heat therapy, co-morbidity management, diet including coffee [2 cups of coffee daily], low alcohol diet, low-fat dairy diet, low fructose diet [especially avoiding sugar-sweetened soft drinks], and low purine diet [avoidance of red meats, seafood], ice therapy, and rest of affected joint).

In April 2009, the U.S. Food and Drug Administration (FDA) approved febuxostat (Uloric), a non-purine analog xanthine oxidase inhibitor and is the first new urate-lowering gout drug in more than 40 years. In August 2009, the FDA approved colchicine (Condylon) for the treatment of acute gout. Several other pharmaceutical companies are also conducting clinical trials to test new drugs for the treatment of acute and chronic gout; one of them is pegloticase, a pegylated recombinant uricase that converts urate into the easily excretable allantoin (Schlesinger 2010).

Yue and associates (2008) described the pharmacokinetics and pharmacodynamics of pegloticase in 40 gout patients. Pegloticase was administered as intravenous infusions every 2 weeks at 4- and 8-mg doses, or every 4 weeks at 8- or 12-mg doses for 12 weeks. Serum pegloticase concentrations, plasma urate, and serum antibody response were determined. Population pharmacokinetics and pharmacodynamics analyses were performed. Data were modeled simultaneously, and co-variates were examined (age, antibody response, body weight, gender, ideal body weight, and race). The dosing regimens to maintain uric acid levels below the therapeutic target of 6 mg/dL were then predicted by the model. The pharmacokinetics were best described by a 1-compartment linear model, while the pharmacodynamics model was fitted as a direct effect of pegloticase on uric acid concentrations with a suppressive maximum effect attributed to drug (E(max)) function. Pegloticase suppressed uric acid levels up to 83 %. Weight only affected clearance and volume of distribution. No co-variates affected pharmacodynamics. Simulation suggests pegloticase administered at 8 mg every 2 or 4 weeks as 2-hour intravenous infusions will maintain uric acid levels well under 6 mg/dL.

In a phase II, randomized study, Sundy et al (2008) evaluated the effectiveness of pegloticase in achieving and maintaining plasma urate levels of less than 6 mg/dl in gout patients in whom other treatments have failed, and assessed the pharmacokinetics and safety of pegloticase. A total of 41 patients were randomized to undergo 12 to 14 weeks of treatment with pegloticase at 1 of 4 dosage levels: (i) 4 mg every 2 weeks, (ii) 8 mg every 2 weeks, (iii) 8 mg every 4 weeks, or (iv) 12 mg every 4 weeks. Plasma uricase
activity, plasma urate, and anti-pegloticase antibodies were measured, pharmacokinetic parameters were assessed, and adverse events were recorded. The mean plasma urate level was reduced to less than or equal to 6 mg/dl within 6 hours in all dosage groups, and this was sustained throughout the treatment period in the 8 mg and 12 mg dosage groups. The most effective dosage was 8 mg every 2 weeks. Twenty-six patients received all protocol doses. The percentage of the patients in whom the primary efficacy end point (plasma urate less than 6 mg/dl for 80% of the study period) was achieved ranged from 50% to 88%. Gout flares occurred in 88% of the patients. The majority of adverse events (excluding gout flare) were unrelated to treatment and were mild or moderate in severity. Infusion-day adverse events were the most common reason for study withdrawal (12 of 15 withdrawals). There were no anaphylactic reactions. Anti-pegloticase antibody, present in 31 of 41 patients, was associated with reduced circulating half-life of pegloticase in some patients. The authors concluded that pegloticase, administered in multiple doses, was effective in rapidly reducing and maintaining plasma urate levels at less than or equal to 6 mg/dl in most patients in whom conventional therapy had been unsuccessful due to lack of response, intolerability, or contraindication.

Hershfield et al (2010) noted that a high plasma urate concentration (PUA), related to loss of urate oxidase in evolution, is postulated to protect humans from oxidative injury. This hypothesis has broad clinical relevance, but support rests largely on in vitro data and epidemiologic associations. Pegloticase therapy generates H(2)O(2) while depleting urate, offering an in vivo test of the antioxidant hypothesis. These researchers showed that erythrocytes can efficiently eliminate H(2)O(2) derived from urate oxidation to prevent cell injury in vitro; during therapy, disulfide-linked peroxiredoxin 2 dimer did not accumulate in red blood cells, indicating that their peroxidase capacity was not exceeded. To assess oxidative stress, these researchers monitored F2-isoprostanes (F2-isoPs) and protein carbonyls (PC), products of arachidonic acid and protein oxidation, in plasma of 26 refractory gout patients receiving up to 5 infusions of pegloticase at 3-week intervals. At baseline, PUA was markedly elevated in all patients, and plasma F2-isoP concentration was elevated in most. Pegloticase infusion rapidly lowered mean PUA to less than or equal to 1 mg/dL in all patients, and PUA remained low in 16 of 21 patients who completed treatment. F2-isoP levels did not correlate with PUA and did not increase during 15 weeks of sustained urate depletion. There also was no significant change in the levels of plasma PC. Because refractory gout is associated with high oxidative stress in spite of high PUA, and profoundly depleting uric acid did not increase lipid or protein oxidation, the authors concluded that urate is not a major factor controlling oxidative stress in vivo.

On September 14, the FDA approved pegloticase (Krystexxa) for the treatment of gout in adults who do not respond to or who can not tolerate conventional therapy. Patients who have failed to normalize serum uric acid (to less than 6 mg/dL) with xanthine oxidase inhibitors at the maximum medically appropriate dose for at least 3 months are deemed refractory. The maximum recommended dosages of allopurinol [Zyloprim] and febuxostat [Uloric] for gout are 800 mg/day and 80 mg/day, respectively. The approval was based on 2 replicate, multi-center, randomized, double-blind, placebo-controlled clinical studies of 6 months duration (a total of 212 patients). Patients were randomized to receive pegloticase every 2 weeks or every 4 weeks or placebo in a 2:2:1 ratio. The primary endpoint in both trials was the proportion of patients who achieved PUA less than 6 mg/dL for at least 80% of the time during month 3 and month 6. The data in both clinical studies demonstrated that a greater proportion of patients treated with pegloticase every 2 weeks achieved urate lowering to below 6 mg/dL than patients receiving placebo. During the
first 6 months of treatment, 47 % (p < 0.001) and 38 % (p < 0.001) of patients in the pegloticase arms of the 2 clinical studies achieved the primary efficacy endpoint, compared with 0 % of patients in the placebo arm.

The effect of treatment with pegloticase on tophi was a secondary efficacy endpoint of the clinical studies and was assessed using standardized digital photography, image analysis and a central reader blinded to treatment assignment. Baseline tophi was found in 71 % of patients. A pooled analysis of data from both clinical studies at month 6 demonstrated that 45 % (p < 0.02) of patients with tophi treated with pegloticase every 2 weeks achieved a complete response, defined as 100 % resolution of at least one target tophus, no new tophus appearing and no single tophus showing progression, compared to 8 % of patients receiving placebo.

Since 25 % of patients in the clinical trials experienced a severe allergic reaction when receiving an infusion of Krystexxa, health care providers should dispense an antihistamine and a corticosteroid to their patients beforehand to minimize the risk of such a reaction. Other reactions included chest pain, constipation, gout flare, injection site bruising, irritation of the nasal passages, nausea and vomiting. The drug is administered to patients every 2 weeks as an intravenous infusion; it should not be administered as an intravenous push or bolus.

Pegloticase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency due to the risk of methemoglobinemia and hemolysis. It is recommended that patients at higher risk for G6PD deficiency (e.g., patients of African or Mediterranean ancestry) be screened for G6PD deficiency before starting pegloticase.

Several pipeline drugs for the treatment of gout include the selective uricosuric drug RDEA594 and various interleukin-1 (IL-1) inhibitors (anakinra, rilonacept, and canakinumab) (Burns and Wortmann, 2011). So et al (2007) stated that monosodium urate crystals stimulate monocytes and macrophages to release IL-1 beta via the NALP3 component of the inflammasome. The effectiveness of IL-1 inhibition in patients with hereditary auto-inflammatory syndromes with mutations in the NALP3 protein suggested that IL-1 inhibition might also be effective in relieving the inflammatory manifestations of acute gout. The effectiveness of IL-1 inhibition was first evaluated in a mouse model of monosodium urate crystal-induced inflammation. Inhibition of IL-1 prevented peritoneal neutrophil accumulation but tumor necrosis factor blockade had no effect. Based on these findings, these investigators performed a pilot, open-labeled study in 10 patients with gout who could not tolerate or had failed standard anti-inflammatory therapies. All patients received 100 mg anakinra daily for 3 days. All 10 patients with acute gout responded rapidly to anakinra. No adverse effects were observed. Blockade of IL-1 appears to be an effective therapy for acute gouty arthritis. The authors stated that these findings need to be confirmed in a controlled study.

In an observational study, Krishnan and colleagues (2012) examined if blood lead levels (BLLs) within the range currently considered acceptable are associated with gout. A total of 6,153 civilians aged 40 years or older with an estimated glomerular filtration rate greater than 10 ml/min per 1.73 m2 were included in this study. Outcome variables were self-reported physician diagnosis of gout and serum urate level. Blood lead level was the principal exposure variable. Additional data collected were anthropometric measures, blood pressure, dietary purine intake, medication use, medical history, and serum creatinine concentration. The prevalence of gout was 6.05% (95 % confidence interval [CI]: 4.49 % to 7.62 %) among patients in the highest BLL quartile (mean of 0.19 µmol/L
[3.95 µg/dL]) compared with 1.76 % (CI: 1.10 % to 2.42 %) among those in the lowest quartile (mean of 0.04 μmol/L [0.89 µg/dL]). Each doubling of BLL was associated with an unadjusted odds ratio of 1.74 (CI: 1.47 to 2.05) for gout and 1.25 (CI: 1.12 to 1.40) for hyperuricemia. After adjustment for renal function, diabetes, diuretic use, hypertension, race, body mass index, income, and education level, the highest BLL quartile was associated with a 3.6-fold higher risk for gout and a 1.9-fold higher risk for hyperuricemia compared with the lowest quartile. The authors concluded that blood lead levels in the range currently considered acceptable are associated with increased prevalence of gout and hyperuricemia. The main drawback of this study was that blood lead level does not necessarily reflect the total body lead burden.

The updated European League Against Rheumatism (EULAR) guideline for the diagnosis and management of gout and hyperuricemia (Hamburger et al, 2011) did not mention testing for BLL. Furthermore, an UpToDate review on "Clinical manifestations and diagnosis of gout" (Becker, 2012) as well as an University of Texas at Austin School of Nursing's clinical practice guideline on "Management of chronic gout in adults" (2012) do not mention measurement of BLL as a diagnostic tool.

In a Cochrane review, Sivera et al (2014) evaluated the benefits and harms of IL-1 inhibitors in acute gout. These investigators searched The Cochrane Library, MEDLINE and EMBASE on June 19, 2013. They applied no date or language restrictions. They performed a hand-search of the abstracts from the European League Against Rheumatism (EULAR) (2009 to 2012) and American College of Rheumatology (ACR) (2009 to 2011) conferences and of the references of all included trials. They also screened the Clinical Trials Registry Platform of the World Health Organization and Clinical Trials Registry Platform of the US National Institutes of Health. These researchers included randomized controlled trials (RCTs) and quasi-randomized clinical trials (controlled clinical trials (CCTs)) assessing an IL-1 inhibitor (e.g., anakinra, canakinumab or rilonacept) against placebo or another active treatment (colchicine, paracetamol, NSAIDs, glucocorticoids (systemic or intra-articular), adrenocorticotropin hormone, a different IL-1 blocking agent or a combination of any of the above) in adults with acute gout. Two review authors independently selected trials for inclusion, assessed the risk of bias and extracted the data. If appropriate, they pooled data in a meta-analysis. They assessed the quality of the evidence using the GRADE approach. These investigators included 4 studies (806 participants) in the review. The studies had an unclear risk of selection bias and low risk of performance and attrition biases. One study each had an unclear risk of detection and selection bias. Three studies (654 participants) compared subcutaneous canakinumab compared with intramuscular triamcinolone acetonide 40 mg in the treatment of acute gout flares of no more than 5-day duration. Doses of canakinumab were varied (10 to 150 mg), but most people (255/368) were treated with canakinumab 150 mg. None of the studies provided data on participant-reported pain relief of 30 % or greater. Moderate-quality evidence indicated that canakinumab 150 mg was probably superior to triamcinolone acetonide 40 mg in terms of pain relief, resolution of joint swelling and in achieving a good treatment response at 72 hours following treatment, but was probably associated with an increased risk of adverse events (AEs). Mean pain (0- to 100-mm visual analog scale (VAS), where 0 mm was no pain) was 36 mm after triamcinolone acetonide treatment; pain was further reduced by a mean of 11 mm with canakinumab treatment (mean difference (MD) -10.6 mm, 95 % CI: -15.2 to -5.9). Forty-four per cent of participants treated with canakinumab had resolution of joint swelling at 72 hours compared with 32 % of participants treated with triamcinolone (risk ratio [RR] 1.39, 95 % CI: 1.11 to 1.74, number needed to treat for an addition...
beneficial outcome (NNTB) 9); 65 % of participants treated with canakinumab assessed their response to treatment as good or excellent compare with 47 % of participants treated with triamcinolone acetonide (RR 1.37, 95 % CI: 1.16 to 1.61, NNTB 6). Function or health-related quality of life (QOL) was not measured. In both groups, 0.7 % of participants withdrew from treatment (RR 1.1, 95 % CI: 0.2 to 7.2); there was 1 death and 1 alteration of laboratory results in each of the treatment groups. Adverse events were more frequent in participants receiving canakinumab (61%) compared with triamcinolone acetonide (51%; RR 1.2, 95% CI 1.1 to 1.4, number needed to treat for an addition harmful outcome (NNTH) 10). Low-quality evidence from one study (152 participants with an acute gout flare of no more than 48 hours’ duration and affecting fewer than 4 joints) comparing rilonacept 320 mg with indomethacin (50 mg 3 times a day for 3 days followed by 25 mg 3 times a day for up to 9 days) indicated that indomethacin may improve pain more than rilonacept at 24 to 72 hours, and there may be no evidence of a difference in withdrawal rates or AEs. The mean change (improvement) in pain from baseline with indomethacin was 4.3 points (measured on a 0 to 10 numerical rating scale, where 0 was no pain); pain was improved by a mean of only 2.5 points with rilonacept (MD 2.52, 95 % CI: 0.29 to 4.75, 25 % less improvement in absolute pain with rilonacept). Inflammation, function health-related QOL and participant global assessment of treatment success were not measured. Rates of study withdrawals due to AEs were low in both groups: 1/75 (1 %) participants in the rilonacept group compared with 2/76 (3 %) participants in the indomethacin group (RR 0.5, 95 % CI: 0.05 to 5.5). Adverse events were reported in 27/75 (36 %) participants in the rilonacept group and 23/76 (30 %) in the indomethacin group (RR 1.2, 95 % CI: 0.8 to 1.9). The authors concluded that moderate-quality evidence indicated that compared with a single suboptimal 40-mg dose of intramuscular injection of triamcinolone acetonide, a single subcutaneous dose of 150 mg of canakinumab probably results in better pain relief, joint swelling and participant-assessed global assessment of treatment response in people with an acute gout flare; but is probably associated with an increased risk of AEs. The cost of canakinumab is over 5,000 times higher than triamcinolone acetonide; however, there are no data on the cost-effectiveness of this approach. Moreover, the authors found no studies comparing canakinumab with more commonly used first-line therapies for acute gout flares such as NSAIDs or colchicine. Low-quality evidence indicated that compared with maximum doses of indomethacin (50 mg 3 times a day), 320 mg of rilonacept may provide less pain relief with a similar rate of AEs.

The Spanish Society of Rheumatology’s clinical practice guidelines for “Management of gout” (SER, 2013) stated the following:

It is not recommended to perform plain radiography, computed tomography (CT) or magnetic resonance imaging (MRI) for the diagnosis of gout (Level of evidence [LE] 2b; Grade of recommendation [GR] B).
Ultrasound assists in the diagnosis of gout; crystal visualization is what establishes the definitive diagnosis (LE 4; GR C).
Ultrasound-guided puncture facilitates obtaining fluid or other samples for the diagnosis of gout (LE 4; GR C).

An UpToDate review on “Clinical manifestations and diagnosis of gout” (Becker, 2014) states that “Ultrasound examination directed to joints or soft tissue deposits is an increasingly promising modality for the early detection and monitoring of therapy for gout”.

12/08/2014
Villaverde et al (2014) performed a systematic literature review of the usefulness of MRI and ultrasound (US) on assessment of treatment response in patients with gout. MEDLINE, EMBASE, Cochrane Library (up to February 2012), and abstracts presented at the 2010 and 2011 meetings of the American College of Rheumatology and European League Against Rheumatism, were searched for treatment studies of any duration and therapeutic options, examining the ability of MRI/US to assess treatment response in gouty patients. Meta-analyses, systematic reviews, randomized clinical trials, cohort and case-control studies and validation studies were included. Quality was appraised using validated scales. There were only 3 US published studies in the literature that analyzed US utility on assessment of response to treatment in patients with gout. All of them were prospective case studies with a small number of patients and they were reviewed in detailed. A total of 36 patients with gout were examined with US. All of them had a baseline serum urate greater than 6 mg/dL. Ultrasound features of gout (double contour sign [DCS], hyper-echoic spots in synovial fluid, hyper-echoic cloudy areas, tophus diameter and volume) achieved significant reduction in patients who reached the objective of uricemia less than or equal to 6mg/dL in all the studies; however, patients in whom levels did not drop below 6 mg/dL had no change of US features of gout. Other parameters evaluated in 1 study included ESR, CRP, number of tender joints (TRN), number of swollen joints, and pain score (SP). All of them decreased with uricemia reduction, but only TRN and SP were statistically significant. No data were found on the value of MRI on treatment response assessment in patients with gout. The authors concluded that the improvement in US features showed concurrent validity with uric acid reduction. According to the published evidence, US can be a useful tool for monitoring treatment of gouty patients, although more research is needed. The value of MRI on treatment response assessment in patients with gout remains to be determined.

Ogdie et al (2014) examined the usefulness of imaging modalities in the classification of gout when compared to mono-sodium urate (MSU) crystal confirmation as the gold standard, in order to inform development of new gout classification criteria. These researchers systematically reviewed the published literature concerning the diagnostic performance of plain film radiography, MRI, US, conventional CT and dual energy CT (DECT). Only studies with MSU crystal confirmation as the gold standard were included. When more than 1 study examined the same imaging feature, the data were pooled and summary test characteristics were calculated. A total of 11 studies (9 manuscripts and 2 meeting abstracts) satisfied the inclusion criteria. All were set in secondary care, with mean gout disease duration of at least 7å€...years. Three features were examined in more than 1 study: (i) DCS on US, (ii) tophus on US, and (iii) MSU crystal deposition on DECT. The pooled (95 % CI) sensitivity and specificity of US DCS were 0.83 (0.72 to 0.91) and 0.76 (0.68 to 0.83), respectively; of US tophus, were 0.65 (0.34 to 0.87) and 0.80 (0.38 to 0.96), respectively; and of DECT, were 0.87 (0.79 to 0.93) and 0.84 (0.75 to 0.90), respectively. The authors concluded that US and DECT show promise for gout classification; but the few studies to-date have mostly been in patients with longstanding, established disease. Moreover, they stated that the contribution of imaging over clinical features for gout classification criteria requires further examination.

CPT Codes / HCPCS Codes / ICD-9 Codes

CPT codes covered if selection criteria are met:
84550
85651
85652

**CPT codes not covered for indications listed in the CPB:**

83655
84560

**Other CPT codes related to the CPB:**

96365
+96366
+96367
+96368
96372
96379

**HCPCS codes covered if selection criteria are met:**

J2507 Injection, Pegloticase, 1 mg

**HCPCS codes not covered for indications listed in the CPB:**

J0638 Injection, canakinumab, 1 mg
J2793 Injection, rilonacept, 1 mg

**ICD-9 codes covered if selection criteria are met:**

274.00 - 274.9 Gout
V77.5 Special screening for gout

**ICD-9 not covered for indications listed in the CPB:**

282.2 Anemias due to disorders of glutathione metabolism [G6PD deficiency]

**The above policy is based on the following references:**


28. Becker MA. Clinical manifestations and diagnosis of gout. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed August 2012.

29. University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program. Management of chronic gout in adults. Austin, TX: University of Texas at Austin, School of Nursing; May 2012.


32. Becker MA. Clinical manifestations and diagnosis of gout. UpToDate [serial online]. Waltham, MA: UpToDate; reviewed August 2014.

