A CLINICAL UPDATE ON GOUT:

Optimizing Care for Patients with Chronic Kidney Disease

Management strategies for:
› Chronic Gout
› Anti-inflammatory Prophylaxis for Gout Flares When Initiating Urate Lowering Therapy
› Acute Gout

INTRODUCTION

Gout has been steadily increasing worldwide, and is now the most common type of inflammatory arthropathy. In the United States alone, its prevalence more than doubled between the 1960s and the 1990s, and it is now estimated at 3.9% of U.S. adults (8.3 million adults—6.1 million men and 2.2 million women). Concomitantly, the prevalence of chronic kidney disease (CKD) has been increasing, with estimates at 14% of adults in the United States, and 8-16% globally. In addition to the overlap of comorbidities associated with both gout and CKD, observational studies demonstrate that CKD is the third most common independent risk factor for gout after obesity and hypertension. Conversely, there is evidence that gout and associated hyperuricemia may independently impair kidney function, aside from the damage caused by uric acid kidney stones.

Due to the global increase in gout, the need for management guidance has led to recommendations from a variety of organizations, most recently the 2012 American College of Rheumatology (ACR) Guidelines for Management of Gout. Managing gout is very challenging, and even more so in the setting of CKD. Therefore, this bulletin will focus on the ACR recommendations and related evidence for safely managing both acute and chronic gout in CKD.
MANAGEMENT STRATEGIES

Because humans lack uricase, they cannot convert the urate generated during purine metabolism into a soluble form, and this can lead to an increased risk for hyperuricemia and monosodium urate crystallization in joints and tissues. Hyperuricemia can be caused by the overproduction of urate, but is more often the result of insufficient renal urate excretion. Because heredity is often seen in primary gout, much research is focused on genes that cause hyperuricemia, notably those that regulate renal urate transport, such as human urate transporter 1 (URAT1). Other non-modifiable risk factors for hyperuricemia and gout include male gender, increasing age, and menopause. Fortunately, effective treatments are available, even for patients with CKD.

Table 1. Comorbidity Checklist

| Appropriate to consider in the clinical evaluation, and if clinically indicated, to evaluate (evidence C for all):* |
| Obesity, dietary factors |
| Excessive alcohol intake |
| Metabolic syndrome, type 2 diabetes mellitus |
| Hypertension† |
| Hyperlipidemia, modifiable risk factors for coronary artery disease or stroke |
| Serum urate–elevating medications† |
| History of urolithiasis |
| Chronic kidney, glomerular, or interstitial renal disease (eg, analgesic nephropathy polycystic kidney disease) |
| In selected cases, potential genetic or acquired cause of uric acid overproduction (eg, inborn error of purine metabolism or psoriasis, myeloproliferative, or lymphoproliferative disease, respectively) |
| Lead intoxication |

* Evidence grades for recommendations: level A = supported by multiple (ie, >1) randomized clinical trials or meta-analyses, level B = derived from a single randomized trial or nonrandomized studies, level C = consensus opinion of experts, case studies, or standard of care.
† The task force panel, without a specific vote, recognized the particular benefits of thiazide diuretics for hypertension.

Table 2. Drugs that Raise Serum Uric Acid

| Drugs that Raise Serum Uric Acid |
| Diuretics (loop and thiazide types) |
| Filgrastim |
| ß-blockers |
| Ribavirin, Interferon |
| Low-dose aspirin |
| Ritonavir |
| Pyrazinamide, ethambutol |
| Darunavir |
| Nicotinic acid, niacin |
| Didanosine |
| Lactic acid |
| Rituximab |
| Cyclosporine |
| Basiliximab |
| Tacrolimus |
| Teriparatide |
| Fructose, xylitol, theophylline |
| Sildenafil |
| Levodopa |
| Diazoxide |
| Cytotoxic agents |

The core principles of nonpharmacologic urate-lowering therapy (ULT) recommendations include:
- losing weight to achieve a healthy body mass index
- following a balanced diet
- exercising to achieve physical fitness
- quitting smoking
- staying well hydrated

Specific diet recommendations from the ACR based on the strongest evidence include: limiting alcohol, particularly beer, as well as meat and seafood; a weaker recommendation was issued for avoiding foods and beverages that are high in fructose. Preventing dehydration has been found to be a simple and effective way of preventing gout attacks, and weight loss may be a meaningful intervention for decreasing serum urate levels in some patients. However, the ACR also recognized that for a great number of patients with gout, diet and lifestyle changes alone are insufficient to achieve serum urate-lowering effects and/or gout attack prophylaxis.

Pharmacologic Strategies

In the setting of chronic gout, hyperuricemia can trigger acute gout flares. Therefore, long-term prophylaxis with ULT is used to maintain serum urate levels below 6 mg/dL, and for some patients below 5 mg/dL, depending upon the severity of signs and symptoms. The ACR emphasizes individualizing care and consideration of comorbidities when striving to find the best urate level for each patient. This is especially prudent for dialysis patients, because urate is easily removed during dialysis, thus decreasing gout, including the metabolic syndrome and cardiovascular disease.
uric acid, another contraindication to this therapy. The ACR recommends considering urine alkalization, urine pH monitoring, and increased fluid intake for reducing the risk of urolithiasis.14

If disease is refractory to monotherapy with either of the XOI options, then a uricosuric agent can be added to an XOI as a second-line approach.14

Pegloticase is an intravenous pegylated uricase recommended only for patients with severe disease who display either intolerance or a refractory response to conventional oral treatments. It has not been studied extensively in CKD and therefore no recommendations were issued for this setting.14,32

Anti-Inflammatory Prophylaxis for Gout Flares When Initiating ULT

The ACR recommends prophylaxis when initiating ULT because the rapid decrease in serum urate can often trigger gout flares. First-line options include low-dose colchicine (0.6 mg orally once or twice daily, with lower doses for moderate-to-severe CKD [eGFR of 15–59 mL/min/1.73 m²] and potential drug-drug interactions). Although low-dose non-steroidal anti-inflammatory drugs (NSAIDs) are recommended by the ACR, they should generally be avoided in CKD.33 Additionally, a stronger level of evidence exists for using colchicine over NSAIDs.14

For patients with severe CKD (CrCl <30 mL/min), the recommended starting dose of colchicine is 0.3 mg/day. For patients on dialysis, the starting dose is 0.3 mg twice a week.34 In CKD, even low-dose colchicine can result in neuromyopathy and bone marrow suppression.35,37 The use of macrolide antibiotics with colchicine has been reported to cause toxicity in CKD, and fatal interactions between clarithromycin and colchicine have also been reported in this population. Caution is essential when prescribing colchicine for the elderly because creatinine levels may appear normal despite significant renal impairment.32

The NKF Kidney Disease Outcomes Quality Initiative recommends that NSAIDs be avoided in people with a GFR <30 mL/min/1.73 m². Prolonged therapy is not recommended in people with GFR <60 mL/min/1.73 m². They should not be used by people taking lithium and avoided in people taking RAAS blocking agents.33 Low-dose prednisone or prednisolone (<10 mg daily) is recommended as a second-line option if first-line agents are ineffective or are contraindicated.14

Figure 1 on page 4 contains the ACR algorithm for treating chronic gout.

Acute Gout

The treatments recommended for acute gout include NSAIDs, colchicine, and corticosteroids, but the ACR does not recommend one therapeutic class over another due to lack of evidence. Drug choice should include consideration of patient comorbidities.35 NSAIDs should generally be avoided in CKD.33

Oral colchicine is another option for patients who cannot tolerate NSAIDs or high doses of corticosteroids. However, colchicine clearance in CKD is greatly reduced, and has...
### Baseline Recommendations for Patients with Diagnosis of Gout

1. **Establish diagnosis of gout**
   - Patient education, with initiation of diet, lifestyle recommendations
   - Consider secondary causes of hyperuricemia (Comorbidity Checklist, see table 1)
   - Consider elimination of nonessential prescription medications that induce hyperuricemia
   - Clinically evaluate gout disease burden (palpable tophi, frequency and severity of acute and chronic symptoms and signs)

### Indications for Pharmacologic ULT

Any patient with established diagnosis of gouty arthritis and:
- Tophus or tophi by clinical exam or imaging study
- Frequent attacks of acute gouty arthritis (≥2 attacks/year)
- CKD stage 2 or worse
- Past urolithiasis

### Select First-Line ULT Agent

Xanthine oxidase inhibitor (XOI):
- **Allopurinol**
- **Febuxostat**

If at least one XOI is contraindicated

Alternative first-line ULT:
- **Probencid**

### Acute Gout Prophylaxis

Initiate concomitant pharmacologic anti-inflammatory gout attack prophylaxis (see p. 3). Treatment duration: The greater of
- At least 6 months
- 3 months after reaching serum urate target appropriate for patient (no tophi)
- 6 months after reaching serum urate target appropriate for patient (one or more tophi)

### Serum Urate Target Achieved?

- **NO**
  - Increase intensity of ULT
  - Re-evaluate serum urate
- **YES**
  - Continue to long-term management of gout

been shown to cause axonal neuropathy, neutropenia, myopathy, rhabdomyolysis, and acute pancreatitis. Along with the recommendation for individualized dosing in CKD, the ACR refers to the FDA guidelines for dose adjustments. In severe CKD (CrCl <30ml/min), the usual acute treatment doses of colchicine are acceptable, but should not be repeated more than once every two weeks. For patients on dialysis, a one-time dose of 0.6 mg is recommended, and should not be repeated more than once every two weeks. Colchicine is contraindicated in patients with renal impairment who are also taking P-gp inhibitors (cyclosporine, ketoconazole, protease inhibitors, and tacrolimus) or strong inhibitors of CYP3A4 (protease inhibitors, imidazoles, and clarithromycin) because of an association with life-threatening and fatal toxicity.

Although the ACR guidelines do not discuss the use of corticosteroids in CKD, they have been found to be an effective and safe alternative to NSAIDs and colchicine in this population. All routes of administration can be effective in acute gout, but the number of joints with active arthritis should be considered when selecting the best approach. According to the ACR, intra-articular corticosteroids may be used in combination with oral corticosteroids, NSAIDs or colchicine.

The ACR guidelines recommend combination therapy for severe acute gout attacks and for patients whose initial response to pharmacologic monotherapy is insufficient. Corticotropin has been found effective for acute gout attacks, but it is expensive and there can be sodium and water retention associated with hormones produced by the adrenal gland, and this may be detrimental to those with CKD.

When there are contraindications to colchicine or NSAIDs, three biologic therapies, anakinra, canakinumab, and rilonacept, have been shown to improve gout pain and inflammation, but more studies are needed to determine their effects on patients with CKD, notably anakinra, which is cleared primarily through the kidneys. These treatments were not included in the ACR guidelines due to lack of randomized trial data on safety and efficacy.

Figure 2 contains the ACR algorithm for treating acute gout.

Figure 2. 2012 ACR Guidelines: Therapy for an Acute Gout Attack

- Acute gouty arthritis should be treated with pharmacologic therapy, ideally within 24 hours of symptom onset.
- Ongoing ULT should not be interrupted during an acute attack.

Assess severity

- Mild-moderate pain, particularly for an attack affecting only 1 or a few small joints, or 1-2 large joints
- Severe pain, particularly for a polyarticular attack or an attack affecting multiple large joints

Monotherapy

- *NSAID (or cox-2 inhibitor)
- Systemic corticosteroids
- Colchicine

Topical ice as needed

Inadequate response

- Switch to alternate monotherapy or add a second agent
- Off-label therapies in clinical trials

Successful outcome

- Patient education
- Consider ULT or adjust ongoing ULT

*NSAIDs generally avoided in CKD

References