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In Practice

Management of Gout and Hyperuricemia in CKD

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Hyperuricemia and gout, the clinical manifestation of monosodium urate crystal deposition, are common in patients with chronic kidney disease (CKD). Although the presence of CKD poses additional challenges in gout management, effective urate lowering is possible for most patients with CKD. Initial doses of urate-lowering therapy are lower than in the non-CKD population, whereas incremental dose escalation is guided by regular monitoring of serum urate levels to reach the target level of < 6 mg/dL (or < 5 mg/dL for patients with tophi). Management of gout flares with presently available agents can be more challenging due to potential nephrotoxicity and/or contraindications in the setting of other common comorbid conditions. At present, asymptomatic hyperuricemia is not an indication for urate-lowering therapy, though emerging data may support a potential renoprotective effect.
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INDEX WORDS: Hyperuricemia; gout; chronic kidney disease; urate-lowering therapy; allopurinol; febuxostat; uricosurics; uricase; colchicine; nonsteroidal anti-inflammatory drugs; glucocorticoids; management; review; renal failure; hemodialysis; kidney transplant; chronic gout; acute gout; gout flare; therapy; treatment.

CASE PRESENTATION

A 58-year-old man with long-standing nontophaceous gout presents to the emergency department with incapacitating pain due to arthritis in the left knee and right first metatarsophalangeal joint. He has chronic kidney disease (CKD), currently stage 3b (estimated glomerular filtration rate [eGFR] of 32 mL/min). His most recent serum urate level is 7.9 mg/dL. He is currently taking allopurinol, 100 mg/d, a dose that was based on his creatinine clearance (CL_{cr}). He also has hypertension, dyslipidemia, and congestive heart failure (CHF). He avoids nonsteroidal anti-inflammatory drugs (NSAIDs) and limits his colchicine prophylactic dose to 1 tablet every other day due to his kidney disease. He has also been told by his cardiologist to avoid prednisone due to possible fluid overload with resultant decompensation of his CHF. This is his third visit to the emergency department within the last year due to gout-related pain.

INTRODUCTION

Gout, the clinical manifestation of crystalline monosodium urate (MSU) deposition, is the most common inflammatory arthritis in adults, especially in men, with increasing prevalence worldwide, ranging from 0.1% to 10% and estimated to be 3.9% in the United States.[1,2] Hyperuricemia, which is biochemically defined as serum urate level ≥ 6.8 mg/dL based on the limit of urate solubility, is even more common. Using population-level sex-specific serum urate distributions to define hyperuricemia, a US study reported a prevalence of 21.2% among men (serum urate > 7.0 mg/dL) and 21.6% among women (serum urate > 5.7 mg/dL).[2]

Because two-thirds of human urate excretion occurs through the kidneys, with the remaining one-third occurring through the gastrointestinal tract, decreased kidney function is associated with hyperuricemia. However, several large epidemiologic studies and small trials suggest that hyperuricemia may potentially be associated with the development and progression of hypertension and CKD.[3] Regardless of which is cause or consequence, the association of CKD with gout and hyperuricemia is common.[4,5] Approximately 20% of adults with gout have CKD stage ≥ 3 compared with 5% of individuals without gout; 15% of adults with hyperuricemia have CKD stage ≥ 3 compared with 3% of individuals without hyperuricemia.[6] The age-standardized prevalence of gout and hyperuricemia increases as kidney function declines, with 24% of adults with eGFRs < 60 mL/min having gout compared with 2.9% of adults with eGFRs ≥ 90 mL/min.[5]

Clinicians therefore are frequently confronted with managing gout in the setting of kidney disease. The management of gout flares can be challenging because of cautions or contraindications in those with diminished kidney function, as well as other common comorbid conditions that occur frequently in CKD. Among adults with CKD stage 3, a total of 87.8% have hypertension, 16.9% have diabetes, 22.9% have ischemic heart disease, and 3.5% have CHF.[7] Similarly, patients with gout, irrespective of kidney

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disease, have high prevalences of these conditions.[6] These comorbid conditions affect therapeutic decision making, particularly for gout flare management, because the agents available have precautions and/or contraindications in these settings. However, there is often unnecessary excessive concern regarding urate-lowering therapy (ULT) in the context of CKD, frequently leading to inadequate management of gout.

CLINICAL CONTEXT

The most typical presentation of gout is the acute onset of a monoarthritis, generally affecting the lower limbs (classically the first metatarsophalangeal joint), lasting 7 to 14 days without therapy, followed by an asymptomatic period of varying duration.[8] Without treatment, flares tend to recur progressively more frequently, last for longer periods, and can become more resistant to treatment for some. In later stages, a chronic inflammatory arthritis can occur with persistent symptoms; often tophi develop with longer duration of disease, although occasionally tophi can be the initial clinical manifestation of gout.[9] In women, the first presentation of gout generally occurs after menopause because of the uricosuric effects of estrogen.[10] Although mono- or oligoarthritis of a lower limb is a common gout flare presentation, other patterns are not infrequent, such as upper-limb involvement and polyarticular flares.[11] Patients with CKD are anecdotally thought to have more variable presentations of their gout flares, including a higher frequency of polyarticular flares. These presentations are also more common among women and elderly individuals and often are associated with diuretic use and CKD.[12-14] Thus, clinicians must remember to consider gout flare in their differential diagnosis of acute joint symptoms in a patient with kidney disease, even if the pattern of joint involvement is not "classic."

The diagnosis of gout is confirmed by the identification of MSU crystals under polarizing microscopy in synovial fluid aspirated from a joint or bursa or in material aspirated from a tophus. This gold-standard confirmation is especially important for patients with CKD, for whom the prevalence of other conditions that mimic gout is also common, such as calcium pyrophosphate deposition disease (formerly known as "pseudogout" and now labeled acute calcium pyrophosphate crystal arthritis), for which the diagnosis is also confirmed by synovial fluid analysis.[15]

In the absence of a crystal-proven diagnosis, other elements of the history and physical examination can be helpful in supporting a diagnosis of gout. Although not intended for use in making diagnoses, the 2015 American College of Rheumatology (ACR)–European League Against Rheumatism classification criteria for gout highlight some of the key factors to consider when evaluating an individual for the possibility of gout.[16,17] Classification criteria are intended for use in research to identify individuals for enrollment into clinical studies and therefore do not necessarily cover the full spectrum of the disease.

MANAGEMENT OF GOUT IN CKD

The management of gout follows the same 4 principles regardless of the presence of CKD: (1) lower serum urate level (ie, manage the hyperuricemia), (2) provide prophylaxis while initiating ULT, (3) treat gout flares, and (4) optimize dietary and lifestyle factors as appropriate. Over a prolonged period with adequate management of hyperuricemia, defined as maintenance of serum urate level < 6 mg/dL or < 5 mg/dL for those with tophaceous gout, gout flares will diminish in frequency and severity, with eventual cessation of flares, and tophi can be prevented and/or resolve.

Management of Hyperuricemia

Hyperuricemia is a necessary, though not sufficient, cause of gout because there are many more individuals with hyperuricemia than with clinically evident gout. Nonetheless, the mainstay and primary focus of gout therapy is to lower elevated serum urate levels to achieve the clinical outcomes that matter to patients: cessation and prevention of flares, resolution and prevention of tophi, and control of inflammatory arthritis for those with chronic gouty arthritis.

In 2012, the ACR published guidelines for the management of gout.[18,19] New in these guidelines was the recommendation to initiate ULT with the first gout flare in patients with CKD stage ≥ 2.[18] The rationale for this new ULT indication is that these patients often have limited options for gout flare management. By initiating ULT earlier, the aim is to avoid the need to treat subsequent gout flares with potentially nephrotoxic or contraindicated agents. For patients with normal eGFRs, indications for ULT continue to include recurrent gout flares (≥ 2 per year), tophi, and nephrolithiasis. In addition, imaging evidence of tophi is a new indication for ULT.

In line with other treatment guidelines, the ACR guidelines noted insufficient evidence to address the management of asymptomatic hyperuricemia.[18,20-22] As reviewed next, there are emerging data regarding the potential benefit of ULT in CKD beyond the context of gout that points to the need for large trials to definitively address this issue.

Nonpharmacologic approaches can be recommended to all patients with gout as adjunctive measures. These include weight loss and avoiding excess intake of purine-rich foods, alcoholic beverages, and fructose-rich beverages. Total prohibition of purine