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

National Kidney Foundation®

INTRODUCTION

Gout has been steadily increasing worldwide, and is now the most common type of inflammatory arthropathy.[1] In the United States alone, its prevalence more than doubled between the 1960s and the 1990s[2,3], 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).[2,4] Concomitantly, the prevalence of chronic kidney disease (CKD) has been increasing, with estimates at 14% of adults in the United States[5], and 8-16% globally.[6] 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.[7,8] Conversely, there is evidence that gout and associated hyperuricemia may independently impair kidney function[9,10], 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[11-13], most recently the 2012 American College of Rheumatology (ACR) Guidelines for Management of Gout.[14,15] 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).[1] Other non-modifiable risk factors for hyperuricemia and gout include male gender, increasing age, and menopause.[1,16] Fortunately, effective treatments are available, even for patients with CKD.

Table 1. Comorbidity Checklist[14]

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 blood pressure control and outcomes in many patients with hypertension.

Chronic Gout

Non-pharmacologic Strategies

Recognizing that improving the comorbidities for gout (eg, hypertension, diabetes, and obesity) can also lead to decreased serum urate levels and gout flares, the ACR guidelines emphasize using nonpharmacologic interventions in all cases of gout .[14] This approach is even more important in CKD because many gout medications can potentially be harmful to the kidneys, and therefore adjuvant methods of decreasing drug burden are helpful. Additionally, CKD shares the same comorbidities found in gout, including the metabolic syndrome and cardiovascular disease.[1,17,18] In order to address these conditions, the ACR developed a comorbidity checklist (Table 1) to help guide patient education, and to encourage individualized care through review of serum urate-elevating medications that could be eliminated or safely substituted, notably thiazide and loop diuretics, niacin, and cyclosporine and tacrolimus.[14] Table 2 includes a list of drugs that raise serum uric acid levels.[19]

Table 2. Drugs that Raise Serum Uric Acid[19]

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 [14,20]

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.[14,20] Preventing dehydration has been found to be a simple and effective way of preventing gout attacks[21], and weight loss may be a meaningful intervention for decreasing serum urate levels in some patients.[20,22] 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.[14,20]

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.[14] 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

urate levels, and research has demonstrated a J-shaped association between mortality and serum urate levels in this population.[23-25]

First-line ULT agents for chronic gout include the xanthine oxidase inhibitors (XOI) febuxostat and allopurinol, with the ACR conferring no preference for one agent over the other. First-line alternatives in the setting of a contraindication or intolerance to at least one XOI include uricosurics.[14]

Febuxostat does not require renal dose adjustment in mild-to-moderate CKD. The usual starting dose is 40 mg/day with a maximum FDA-approved dose of 80 mg/day.[26] Three randomized trials have demonstrated significantly greater urate-lowering efficacy of febuxostat at 80 mg/day in comparison to either febuxostat 40 mg/day or to allopurinol 300 mg/day, while also conferring equivalent safety in patients with mild-to-moderate CKD (eGFR of 30-89 mL/min/1.73 m^2).[27-29] Because insufficient evidence exists on its safety in CKD stage 4 or worse (eGFR of ≤15 mL/min/1.73 m^2), no recommendation was issued for using febuxostat in this setting.[14] Several cases of neutropenia associated with the use of febuxostat in CKD have recently been reported.[30]

Allopurinol is another first-line XOI option that the ACR recommends, but with a starting dose no greater than 100 mg/day, and in CKD stage 4 or worse, no greater than 50 mg/day. Doses can be increased above 300 mg/day, even in patients with CKD, as long as appropriate monitoring and patient education is provided. The ACR does not recommend the traditional algorithm used to adjust doses according to kidney function, but rather to start therapy with lower doses and gradually titrate upward every 2-5 weeks from the allopurinol maintenance dose to the maximum dose needed to achieve the serum urate target. This approach may reduce the risk of early gout flares after ULT initiation, as well as the occurrence of allopurinol-induced hypersensitivity (AHS) reactions.[14] AHS can cause symptoms of Stevens-Johnson syndrome and toxic epidermal necrolysis, as well as systemic abnormalities such as eosinophilia, vasculitis, rash, and end organ disease.[31] AHS is rare, but results in significant mortality of 20-25%.[14] A combination of CKD and thiazide diuretics can increase the risk of AHS. In patients who are at higher risk for AHS (eg, Koreans with stage 3 or worse CKD [eGFR of ≤59 mL/min/1.73 m^2], and those of Han Chinese and Thai descent), a polymerase chain reaction (PCR)-based HLA-B*5801 screening is recommended before initiating therapy.[14]

Probenecid is the first choice for uricosuric ULT, but it is not recommended for patients with a creatinine clearance <50 ml/min.[14] Alternative agents with uricosuric effects also suggested by the ACR include fenofibrate or losartan. A history of urolithiasis is a contraindication to first-line uricosuric ULT monotherapy. It is recommended that urinary uric acid be measured before initiating uricosuric ULT because increased levels indicate overproduction of uric acid, another contraindication to this therapy. The ACR recommends considering urine alkalinization, 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 m^2] 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 <30ml/min/1.73m^2. Prolonged therapy is not recommended in people with GFR <60ml/min/1.73m^2. 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]

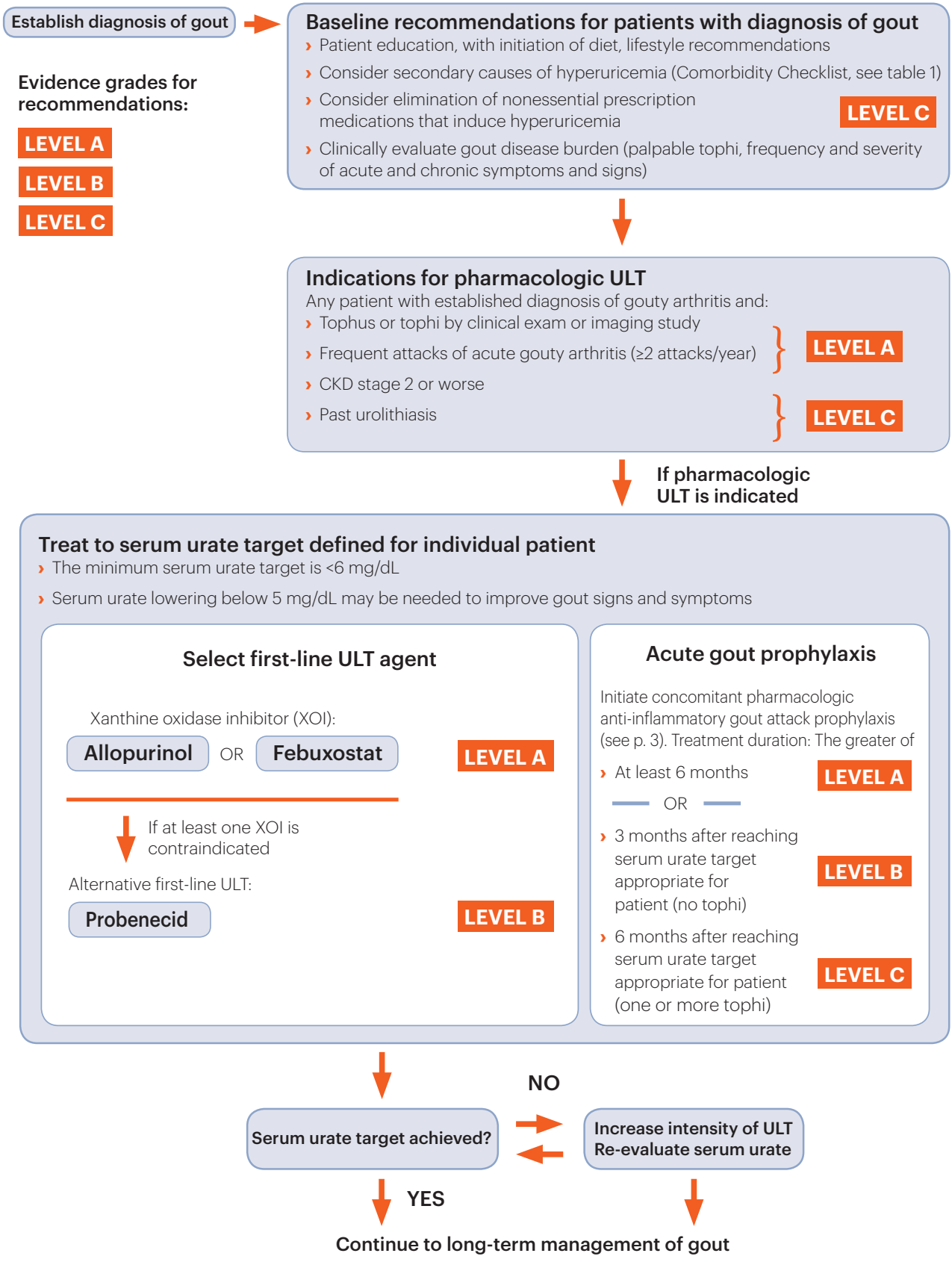
Figure 1 on page 4 contains the ACR algorithm for treating chronic gout.

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.[15] 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

Figure 1. 2012 ACR Guidelines for Chronic Gout: Baseline Recommendations, Including Indications for Urate Lowering Drug Therapy[14]



Adapted from Khanna D et al. *Arthritis Care Res.* 2012;64:1431-1446.

been shown to cause axonal neuropathy, neutropenia, myopathy, rhabdomyolysis, and acute pancreatitis.[32,35-37] 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.[34]

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.[38,39] 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.[15]

The ACR guidelines recommend combination therapy for severe acute gout attacks and for patients whose initial response to pharmacologic monotherapy is insufficient.[15]

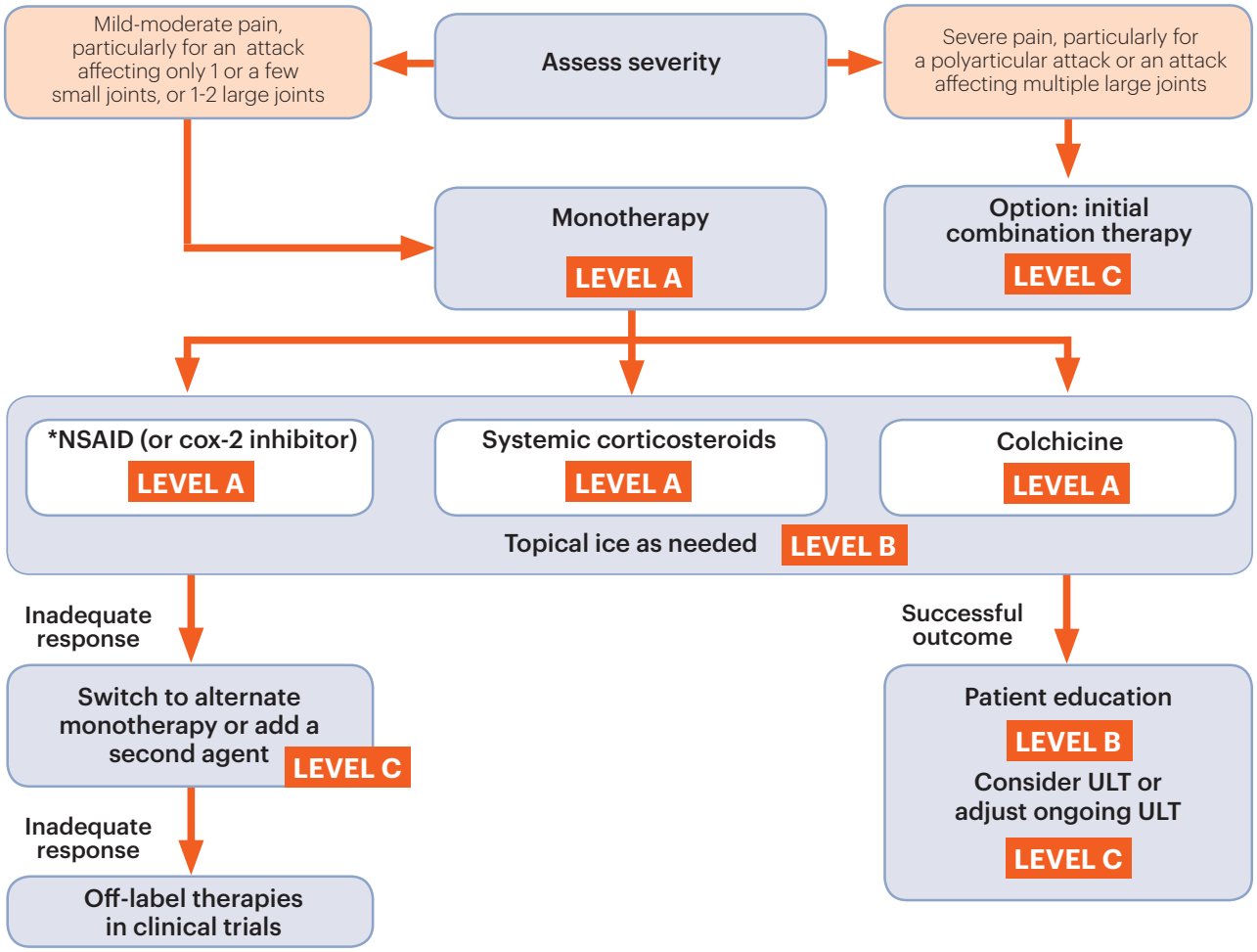
Corticotropin has been found effective for acute gout attacks, but it is expensive and there can be sodium and water retention associated with hormones produced by the adrenal gland, and this may be detrimental to those with CKD.[35,40]

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.[32,41] 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[15]

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



**NSAIDs generally avoided in CKD*

Adapted from Khanna D et al. *Arthritis Care Res.* 2012;64:1447-1461.

References

1. Roddy E, Doherty M. Epidemiology of gout. *Arthritis Res Ther.* 2010;12:223.
2. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007-2008. *Arthritis Rheum.* 2011;63:3136-3141.
3. Lawrence RC, Felson DT, Helmick CG, et al. The National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: part II. *Arthritis Rheum.* 2008;58:26-35.
4. Centers for Disease Control and Prevention (CDC). National Center for Health Statistics (NCHS). *National Health and Nutrition Examination Survey Questionnaire (NHANES) 2007-2008.* Hyattsville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2009. Available at: http://wwwn.cdc.gov/nchs/nhanes/search/nhanes07_08.aspx. Accessed May 10, 2014.
5. U.S. Renal Data System (USRDS). *USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States.* Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2013.
6. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. Global kidney disease 3. Available at: www.thelancet.com. Published online May 31, 2013. http://dx.doi.org/10.1016/50140-6736(13)60687-X.
7. Krishnan E. Chronic kidney disease and risk of incident gout among middle-aged men: a seven-year prospective observational study. *Arthritis Rheum.* 2013;65:3271-3278.
8. Juraschek SP, Kovell LC, Miller ER, et al. Association of kidney disease with prevalent gout in the United States in 1988-1994 and 2007-2010. *Semin Arthritis Rheum.* 2013;42:551-561.
9. Obermayr RP, Temml C, Gutjahr G, et al. Elevated uric acid increases the risk for kidney disease. *J Am Soc Nephrol.* 2008;19:2407-2413.
10. Feig DI. Uric acid: a novel mediator and marker of risk in chronic kidney disease? *Curr Opin Nephrol Hypertens.* 2009 Nov;18(6):526-530.
11. Hamburger M, Baraf HSB, Adamson Thomas C. 2011 Recommendations for the diagnosis and management of gout and hyperuricemia. *Postgrad Med.* 2011;123:3-36, suppl. 1.
12. Jordan KM, Cameron JS, Snaith M, et al. British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group (SGAWG). British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of gout. *Rheumatology.* 2007 Aug;46(8):1372-1374. Epub: 2007 May 23. doi: 10.093/rheumatology/kem056b.
13. Sivera F, Andres M, Carmona L, et al. Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systematic literature review and expert opinion of a broad panel of rheumatologists in the 3e Initiative. *Ann Rheum Dis.* 2013;0:1-8.
14. Khanna D, Fitzgerald JD, Khanna PP, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1: systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis Care Res.* 2012;64:1431-4446.
15. Khanna D, Khanna PP, Fitzgerald JD. 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and anti-inflammatory prophylaxis of acute gouty arthritis. *Arthritis Care Res.* 2012;64:1447-1461.
16. Hak AE, Curhan GC, G Rodstein F, et al. Menopause, post-menopausal hormone use, and risk of incident gout. *Ann Rheum Dis.* 2010;69:1305-1309.
17. Choi HK, Ford ES, Li C, et al. Prevalence of the metabolic syndrome in patients with gout: the Third National Health and Nutrition Examination Survey (NHANES). *Arthritis Rheum.* 2007;57:109-115.
18. Choi HK, Curhan G. Independent impact of gout on mortality and risk for coronary heart disease. *Circulation.* 2007;116:894-900.
19. Moriwaki Y. Effects on uric acid metabolism of the drugs except the antihyperuricemics. *J Bioequiv Availab.* 2014;6(1):10-17. doi: 10.4172 jbb.1000173
20. Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. *Curr Opin Rheum.* 2010;22:165-172.
21. Neogi T, Chen C, Chaisson C, et al. Drinking water can reduce the risk of recurrent gout attacks [abstract]. *Arthritis Rheum.* 2009;60 Suppl 10:2038. doi: 10.1002/art.27110
22. Zhu Y, Zhang Y, Choi HK. The serum urate-lowering impact of weight loss among men with a high cardiovascular risk profile: the Multiple Risk Factor Intervention Trial. *Rheumatology.* 2010;49:2391-2399.
23. Lee SMK, Lee AL, Winters TJ, et al. Low serum uric acid level is a risk factor for death in incident hemodialysis patients. *Am J Nephrol.* 2009;29:79-85
24. Hsu S, Pai M, Peng C, et al. Serum uric acid levels show a "J-shaped" association with all-cause mortality in haemodialysis patients. *Nephrol Dial Transplant.* 2004;19:457-462.
25. Sulliman ME, Johnson RJ, Garcia-Lopez E, et al. "J-shaped" mortality relationship for uric acid in CKD. *Am J Kidney Dis.* 2006;48:761-771.
26. Uloric [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; January 2011.
27. Becker MA, Schumacher HR, Wortmann RL. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *N Engl J Med.* 2005;353:2450-2461.
28. Schumacher HR, Becker MA, Wortmann RL. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. *Arthritis Rheum.* 2008;59:1540-1548.
29. Becker MA, Schumacher HR, Espinoza LR, et al. The urate-lowering efficacy and safety of febuxostat in the treatment of the hyperuricemia of gout: the CONFIRMS trial. *Arthritis Res & Ther.* 2010;12:R63.
30. Kobayashi S, Ogura M, Hosoya T. Acute neutropenia associated with initiation of febuxostat therapy for hyperuricaemia in patients with chronic kidney disease. *J Clin Pharm Ther.* 2013;38:258-261.
31. Arellano F, Sacristan J. Allopurinol hypersensitivity syndrome: a review. *Ann Pharmacother.* 1993;27:337-343.
32. Curiel RV, Guzman NJ. Challenges associated with the management of gouty arthritis in patients with chronic kidney disease: a systematic review. *Sem Arthritis Rheum.* 2012;42:166-178.
33. Inker LA, Astor BC, Fox CH, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. *Am J Kidney Dis.* 2014;63:713-735.
34. Colcrys [package insert]. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; June 2012.
35. El-Zawawy H, Mandell BF. Managing gout: how is it different in patients with chronic kidney disease? *Cleveland Clin J Med.* 2010;77:919-928.
36. Kund RW, Duncan G, Watson D, et al. Colchicine myopathy and neuropathy. *N Engl J Med.* 1987;316:1562-1568.
37. Wilbur K, Makowsky M. Colchicine myotoxicity: case reports and literature review. *Pharmacotherapy.* 2004;24:1784-1792.
38. Janssens HJ, Lucassen PL, Van de Laar FA, et al. Systemic corticosteroids for acute gout. *Cochrane Database Syst Rev.* 2008;Apr 16(2):CD005521.
39. Man CY, Cheung IT, Cameron PA, et al. Comparison of oral prednisolone/paracetamol and oral indomethacin/paracetamol combination therapy in the treatment of acute gout-like arthritis: a double-blind, randomized, controlled trial. *Ann Emerg Med.* 2007;49:670-677.
40. Connell JM, Whitworth JA, Davies DL, et al. Effects of ACTH and cortisol administration on blood pressure, electrolyte metabolism, atrial natriuretic peptide and renal function in normal man. *J Hypertens.* 1987;5:425-433.
41. Yang BB, Baughman S, Sullivan JT. Pharmacokinetics of anakinra in subjects with different levels of renal function. *Clin Pharmacol Ther.* 2003;74:85-94.

Sponsored by
Takeda Pharmaceuticals, USA

National Kidney Foundation®

30 East 33rd Street
New York, NY 10016
800.622.9010
www.kidney.org

Awareness. Prevention. Treatment.