Philippine Clinical Practice Guidelines for the Management of Gout 2008

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ABSTRACT

Objective: Gout is the most prevalent form of arthritis afflicting Filipinos. The diagnosis and overall management need further improvement especially among medical practitioners. Our study aims to develop evidence-based guidelines for general medical practitioners on the management of uncomplicated gout with the overall goal of improving the standard of care of
patients with gouty arthritis.

Methodology: The Technical Review Committee (TRC) of the Philippine Rheumatology Association (PRA) Gout Special Interest Group (SIG) conducted a literature search relating to management issues on all phases of gout from years 1980 to 2007 using databases including Medline, Ovid, Lilacs, Cochrane Central Register of Controlled Trials (CENTRAL). The GRADE system in rating quality of evidence and strength of recommendation was used. A multidisciplinary panel voted and approved the final recommendations during an en banc meeting.

Results: Nine recommendations for the management of uncomplicated gouty arthritis were developed based on evidence from the literature and consensus among experts and key stakeholders. Concerns regarding the initiation and maintainance of urate lowering therapy, target serum uric acid levels, treatment of acute gout, lifestyle and dietary modifications, comorbidities associated with gout such as cardiovascular disease were addressed.

Keywords: practice guidelines, gouty arthritis

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INTRODUCTION

Gout is the most prevalent form of arthritis among the Filipinos. The prevalence of gout is 1.6% (1), a distinctive uptrend compared to 1991 when the prevalence was 0.5% (2), and in 1997 when the prevalence was 0.13% (3). Despite known quality indicators for treatment of gout (4), there is poor adherence of physicians to these indicators (5). Interestingly, inappropriate management of gout is a frequent occurrence even with physician consultation (6).

The Philippine Rheumatology Association (PRA) sought to establish evidence-based guidelines with the goal of improving the standards of care for patients with gout. It is intended to assist medical care providers in making decisions on the care of these patients based on the best available evidence. Guidelines were specifically sought to address the following issues: to assess the role, safety and effectiveness of available therapies including colchicine, corticosteroids, allopurinol; to establish the role of non-pharmacologic measures including dietary modification, alcohol cessation, ice compress; to define the importance of addressing hyperuricemia; to address the role of other hypouricemic agents such as losartan and fenofibrate; to emphasize cardiovascular and renal co-morbidities associated with uncontrolled gout and hyperuricemia. Issues related to the diagnosis of gout and management of complicated cases of gout are not included in this guideline. The full-length text of the guidelines can soon be found on rheumatology.org.ph.

METHODOLOGY

The PRA Gout Steering Committee convened a technical review committee to search for and grade the available evidence related to the management of all phases of gout.

A search for studies published in English between 1980 and 2007 was done: systematic reviews, meta-analysis, randomized controlled trials (RCTs), open label trials, cohort studies on general population, and case reports on different phases of gouty arthritis. Authors of irretrievable published articles were contacted. Full articles and abstracts were appraised.

The following electronic databases used included: PUBMED, METACRAWLERS, GOOGLE SCHOLAR, OVID, MEDLINE, Cochrane Central Regions of Controlled Trials (CENTRAL), the Cochrane Library Issue 3, 2004, LILACS. All related reference lists of retrieved trials/studies were likewise hand-searched. The following search terms were used: asymptomatic hyperuricemia, hyperuricemia, allopurinol hypersensitivity, allopurinol hypersensitivity syndrome, allopurinol, metabolic syndrome, cardiovascular events (congestive heart failure, hypertension, stroke), diabetes mellitus, renovascular events (end stage renal disease), purine diet, gout/gouty arthritis, losartan, fenofibrate, colchicine, nonsteroidal anti-inflammatory drugs (NSAID), selective cyclo-oxygenase 2 (COX-2) inhibitors, tophi, tophaceous gout, intra-articular/ oral/ systemic corticosteroid/ glucocorticoid. Data abstraction was performed independently by at least 2 separate investigators. Disagreements were settled through discussions. The GRADE system (7,8) was utilized in evaluating the quality of evidence and strength of recommendation. Panel members based their recommendations on the merits of each evidence, expert opinion, and local applicability and affordability of treatment approaches.

Recommendations were then presented to a multidisciplinary panel comprised of representatives from the Department of Health, and nine other medical societies (Philippine College of Physicians, Philippine Society of Nephrology, Philippine Pharmacists Association, Philippine Heart Association, Philippine Society of Endocrinology and Metabolism, Philippine Academy of Family Physicians, Nutritionist-Dietitian Association of the Philippines, and Philippine Academy of Rehabilitation Medicine), and a patient with gout. During an en banc meeting, nominal group technique was employed. Panel members cast their votes to finalize the recommendations.

RESULTS

Phase 1: Asymptomatic Hyperuricemia

Hyperuricemia is defined as serum uric acid (SUA) level exceeding the limit of urate solubility in the plasma, which is 7 mg/dl (416 umol/L) in men and 6 mg/dl (357 umol/L) in pre-menopausal women. Asymptomatic hyperuricemia is defined as hyperuricemia in the absence of gouty arthritis and uric acid nephrolithiasis. The prevalence of hyperuricemia is 37.8% in males and 18% in females (1).

Table 1. Philippine Clinical Practice Guidelines for the Management of Gout

Recommendations	Level of Evidence
PHASE 1: Asymptomatic Hyperuricemia	
1. In the general population, asymptomatic hyperuricemia should not be routinely treated with allopurinol. Well-known associated risk factors of hyperuricemia, ie. dyslipidemia, obesity, metabolic syndrome, psoriasis, malignancies, congestive heart failure, should foremost be addressed.	C
2. Lifestyle changes recommended include the following:	
• Adherence to animal or vegetable protein diet as well as intake of dairy products is recommended.	C
• Avoidance of a high meat and seafood diet and alcoholic beverages most especially beer should be prescribed.	B
• Low impact and aerobic exercise at least 45 minutes 4 times a week, intake of at least 8 glasses of water a day, and maintenance of appropriate BMI, are likewise advised.	C, expert opinion
PHASE 2: Acute Gout	
3. In the absence of contraindications , ie. gastrointestinal ulcers or renal impairment, the use of colchicine, traditional non-steroidal anti-inflammatory drugs (NSAIDs), OR selective cyclo-oxygenase 2 (COX-2) inhibitors is recommended for the treatment of acute gouty arthritis.	A
• The expert panel recommends that colchicine should not exceed 4 tablets in divided doses per day.	B
• Prednisone, initially at 30 mg and rapidly tapered over 6 days, can be given as alternative if colchicine, traditional NSAIDs or COX-2 inhibitors are contraindicated or not tolerated by the patient.	B
• Absence of response after a week should prompt reevaluation of the diagnosis and referral to a rheumatologist.	C, expert opinion
4. Ice compress is recommended in combination with pharmacologic agents for relief of joint pain and swelling of acute gouty arthritis.	B
PHASE 3-4: INTERCRITICAL AND CHRONIC TOPHACEOUS GOUT	
5. Serum uric acid (SUA) level should be reduced to and maintained at < 6 mg/dl (0.36 mmol/L).	B
6. Continuous long-term therapy with allopurinol is advised to achieve a target serum uric acid level of < 6 mg/dl.	A
7. Allopurinol should be started at 100 mg/day 2 weeks after the pain and swelling of gouty arthritis has subsided. The dose is titrated by 50-100 mg/day every 2 to 4 weeks to achieve serum uric acid < 6 mg/dl. The maximum dose of allopurinol is 300 mg/day. Referral to rheumatologist is recommended if SUA persistently remains > 6 mg/dl despite maximum dose of allopurinol. SUA and serum creatinine should be periodically monitored.	C

A – high level of evidence; B, moderate level of evidence; C, low level of evidence

Recommendations	Level of Evidence
PHASE 3-4: INTERCRITICAL AND CHRONIC TOPHACEOUS GOUT *(Continued)*	
8. Colchicine should be used at 0.5 mg/tab OD – BID to prevent gout flares when initiating allopurinol. This should be maintained for 3-6 months from the last occurrence of gout flare and after the optimal SUA target is achieved. In the event that adverse events like diarrhea occur, a lower dose of colchicine should be used. NSAIDs should not be used for prevention of gout flares.	A
9. Dietary modification (to promote weight loss) and avoidance of alcohol should be prescribed.	B
Low impact exercises (walking, biking, swimming, ballroom dancing) may also be advised.	C

A – high level of evidence; B, moderate level of evidence; C, low level of evidence

Hyperuricemia is a central feature of gout but does not inevitably and absolutely cause it. The development of gout seems to be directly related to the level of hyperuricemia, however, it is not absolute. The cumulative incidences of gout up to 5 years are increased in direct relation to elevated levels of SUA (9,10). Hyperuricemia is also associated with hypertension (11,12,13), obesity (12), and albuminuria in the presence of renal disease (14). One prospective study did show that allopurinol treatment may result in improvements in blood pressure and creatinine clearance but not in proteinuria; however, this study included patients with normal renal function and allopurinol dose was not specified (15). In another trial involving patients with chronic kidney disease, allopurinol treatment resulted in improvements in renal disease but without significant improvements in hypertension and proteinuria (16). Further studies are needed to confirm the benefit of allopurinol in decreasing cardiovascular and renal risks in the general population.

The relative risks (RR) for incident gout and hyperuricemia were significantly increased with intake of meat, seafood, alcohol especially beer and spirits (17-20). Low to moderate purine diet may reduce SUA and risk of gout while moderate consumption of purine-rich vegetable, low fat dairy products, low fat-yoghurt were not associated with increased risk of gout (18). High protein intake may increase risk of hyperuricemia (19).

The expert panel further recommended low impact and aerobic exercises at least 45 minutes 4 times a week, intake of at least 8 glasses of water a day, and maintenance of THE appropriate BMI (21).

Phase 2: Acute Gouty Arthritis

Acute gouty arthritis is defined in accordance with the 1977 American College of Rheumatology (ACR) criteria for the classification of acute attack of primary gout (22).

There is no evidence demonstrating benefit with a hierarchal order in the use of medications for acute gout. The Philippine guidelines recommend that the choice of drug for acute gouty arthritis be individualized taking into consideration drug efficacy, safety, and cost.

Studies comparing indomethacin with other NSAIDs have shown comparable efficacy in reducing pain (23-25). Etoricoxib, a selective cyclooxygenase-2 inhibitor, is also effective but with less gastrointestinal adverse events (26). "Short course oral steroids" is defined as 30 mg oral prednisone tapered off over 6 days. Corticosteroids are useful for patients who have contraindications to therapy with NSAIDs (27, 28). Parenteral corticosteroids may be used among those who cannot take oral corticosteroids. Colchicine hastens the resolution of an acute gout attack (29). However due to significant gastrointestinal toxicity, the expert panel recommends limiting

colchicine to 0.5mg/tab 1 tab BID-QID. Ice compress along with corticosteroids and colchicine is also beneficial (30).

Phases 3 and 4: Intercritical Gout and Chronic Tophaceous Gout

Intercritical Gout, referred to as "interval gout", applies to the asymptomatic periods between gouty attacks. Chronic Tophaceous Gout (CTG) occurs in untreated gouty arthritis, characterized by persistent low grade inflammation of joints with sporadic flares. Joint deformities seen are due to deposition of massive urate crystals forming visible tophi (29).

ULT is indicated in the following situations: recurrent attacks, radiographic changes, tophaceous deposits, renal insufficiency, nephrolithiases (26). Likewise, individuals with high serum urate (>13 mg/dl) even without clinical signs of gout and high renal urate excretion should be candidates for ULT to prevent uric acid nephrolithiases (31).

There is considerable data showing a direct benefit in lowering SUA on the course of gout. Fifty-six percent of patients who achieved SUA <6 mg/dl had depletion of urate crystals from their knee joints and experienced less gout flares annually compared to patients unable to achieve this target (32). In a review of 267 patients followed up for 3 years, infrequent gouty attacks were associated with reduced SUA concentrations (33). SUA levels between 4.6–6.6 mg/dl is associated with fewer gout attacks (34) and faster rate of reduction of size of tophi (35). Tophaceous deposits were persistent in 37% of those whose urate values remained >6 mg/dl (35). SUA > 6 mg/dl is associated with 59% higher chances of gout flare (32).

Lowering SUA to <6 mg/dl has likewise shown reduction of tophi size (35). A prospective study revealed an inverse relationship of SUA levels and rate of tophi reduction (32). Although "normal" ranges of SUA levels differ among, laboratory facilities across the country, due to lack of standardization, optimal SUA levels of gout patients should be kept at <6mg/dl.

Allopurinol is a xanthine oxidase inhibitor considered to be the cornerstone of the clinical management of gout and other conditions associated with hyperuricemia. It is used in both urate overproducers and underexcretors. It is the preferred urate-lowering drug in several countries (36, 37) and is the only drug available in this class in the Philippines. It has been found to have the lowest incremental cost-effectiveness ratio (38). Despite its widespread use, there is a dearth of clinical trials addressing its long term efficacy and safety for gout. Data from randomized clinical trials showed that allopurinol given at a daily dose of 200–600 mg for 12-30 months reduced SUA levels by 3.16 to 4.8 mg/dl with consequent reduction in gout flares and resolution of tophi in some patients (39-40). Additional benefits on renal function among chronic gout patients revealed preserved or improved creatinine clearance after 12-24 months of therapy (39).

Most clinical studies advocate continuous use over intermittent use of urate-lowering therapies. SUA rise rapidly to pretreatment levels after drug discontinuation with recurrence of gout flares and tophi (41-42). One small prospective 5-year follow-up study of gout suggested intermittent therapy could be offered to patients with good SUA control (43).

Recent studies have evaluated the adjunctive benefits of fenofibrates and losartan among patients with gout. In the absence of large trials, these may be considered for the treatment of concomitant dyslipidemia and hypertension among gout patients. Other uricosuric agents (sulfinpyrazone, benzbromarone and probenecid), are not being dispensed locally. New drugs are still undergoing clinical trials. Febuxostat, an oral non-purine selective inhibitor of xanthine oxidase, as of May 2008 has been approved for use in the European Union, and is currently undergoing further evaluation in the United States by the Food and Drug Administration (FDA). PEG-uricase, a recombinant mammalian urate oxidase, also shows promise in treating gout-related hyperuricemia.

Conclusions

We have developed the first clinical practice guidelines in the Philippines for management of uncomplicated gouty arthritis based on best available evidence and best clinical practice. Nine key recommendations were extensively evaluated. Updates in management issues will be integrated as deemed necessary in the next 3 or more years.

References

1. Dans LS, Salido EO, Penserga EG, Navarra SV for the 2003 NNHeS Group. National Nutrition and Health Survey (NNHeS) : Prevalence of rheumatic diseases among adult Filipinos. Phil J Int Medicine 2006; 44:297-303.
2. Wigley RD, Manahan L, Muirden KD. Rheumatic Disease in a Philippine Village II: A WHO-APLAR COPCORD study, Phase II and III. Rheumatol Int 1991;152-61.
3. Dans LF, Tankeh-Torres S, Amante CM, Penserga EG. The prevalence of Rheumatic Diseases in a Filipino Urban Population: A WHO-ILAR COPCORD Study. J Rheumatol 1997; 24:1814-9.
4. Mikuls TR, MacLean CH, Olivieri J, et al. Quality of care indicators for gout management. *Arthritis Rheum*. 2004; 50:937-43.
5. Hamijoyo L, Li-Yu J, Torralba TP. A Survey of clinical management of gout among Filipino physicians. Phil J Int Med 2008; 46:51-5
6. Neogi T, Hunter DJ, Chaisson CE, Allensworth-Daview D, Zhang Y. Frequency and predictors of inappropriate management of recurrent gout attacks in a longitudinal study. 2006; 33:104-9.
7. GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004; 328:1490-7
8. Atkins D, Briss PA, Eccles M, Flottorp Signe, et al. Systems for grading the quality of evidence and the strength of recommendations II: Pilot study of a new system. BMC Health Services Research 2005; 5:25-36.
9. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med 1987;82:421-426.
10. Lin KC, Lin HY, Chou P. The interaction between serum uric acid level and other risk factors for the development of gout among asymptomatic hyperuricemic men in a prospective study. J Rheumatol 2000;27:1501-1505.
11. Dans LF. Association between hypertension and serum uric acid among Filipinos undergoing executive check-ups. Phil J Internal Medicine 2003; 41:115-21.
12. Huang-Biagtan H, Mejia AD, Gomez LA, Montemayor ES. NNHeS 2003: Relationship of serum uric acid and blood pressure among adult Filipinos. (Data unpublished)
13. Li-Yu J. Relationship of serum uric acid and cardiovascular and renal risk factors. (Data unpublished)
14. Huang-Biagtan H, Mejia AD, Gomez LA, Montemayor E. NNHeS 2003: Relationship of hyperuricemia and albuminuria among adult Filipinos. (Data unpublished)
15. Kanbay M, Ozkara A, Selcoki Y, Isik B, et al. Effect of treatment of hyperuricemia with allopurinol on blood pressure, creatinine clearance, and proteinuria in patients with normal renal functions. Int Urol Nephrol 2007; 39:1227-1233.
16. Siu YP, Leung KT, Tong MKH, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower SUA level. Am J Kidney Dis 2006; 47:51-9.
17. Peixoto MRG, Monego ET, Jardim PCV, Carvalho MM, et al. Diet and medication in the treatment of hyperuricemia in hypertensive patients. Arq Bras Cardiol 2001; 76:468-72.
18. Choi K, Atkinson K, Karlson EW, Willett W, et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. N Engl J Med 2004; 350:1093-1103.
19. Choi HK, Liu S, Curhan G. Intake of purine rich foods, protein, and dairy products, and relationship to serum levels of uric acid. Arthritis Rheum 2005; 52:283-9.
20. Choi HK, Atkinson K, Karlson EW, Willett W, et al. Alcohol intake and risk of incident gout in men: a prospective study. Lancet 2004; 363:1277-81.
21. The World Health Organization Western Pacific Region, the International Association for the Study of Obesity, and the International Obesity Task Force. Asia-Pacific Perspective Redefining Obesity and its Treatment. Sydney Health Communication Australia PTY Limited, 2000.
22. Wallace SL, Robinson H, Masi AT, Decker JL, et al. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977; 20:895-900.
23. Shrestha M, Morgan DL, Moreden JM, Singh R et al. Randomized double-blind comparison of the analgesic efficacy of intramuscular ketorolac and oral indomethacin in the treatment of acute gouty arthritis. Ann Emerg Med 1995; 26:682-6.
24. Maccagno A, Di Giorgio E, Romanowicz A. Effectiveness of etodolac ('Lodine') compared with naproxen in patients with acute gout. Curr Med Res Opin 1991; 12:423-9.
25. Altman RD, Honig S, Levin JM, Lightfoot RW. Ketoprofen versus indomethacin in patients with acute gouty arthritis: a multicenter,

double blind comparative study. J Rheumatol 1988;15:1422-6.
26. Schumacher HR Jr, Boice JA, Daikh DI, Mukhopadhyay S et al. Randomised double blind trial of etoricoxib and indomethacin in treatment of acute gouty arthritis. BMJ 2002; 324:1488-92.
27. Werlen D, Gabay C, Vischer TL. Corticosteroid therapy for the treatment of acute attacks of crystal-induced arthritis: an effective alternative to nonsteroidal inflammatory drugs. Rev Rheum Engl Ed 1996; 63:248-254.
28. Alloway JA, Moriarty MJ, Hoogland YT, Nashel DJ. Comparison of triamcinolone acetonide with indomethacin in the treatment of acute gouty arthritis. J Rheumatol 1993; 20:111-3.
29. Ahern MJ, Reid C, Gordon TP, McCredie M, et al. Does colchicine work? The results of the first controlled study in acute gout. Aust NZ J Med 1987; 17:301-4.
30. Schlesinger N, Detry MA, Holland BK, Baker DG, et al. Local ice therapy during bouts of acute gouty arthritis. J Rheumatol. 2002; 29:331-4.
31. Willburger RE, Mysler E, Derbot J, Jung T et al. Lumiracoxib 400 mg once daily is comparable to indomethacin 50 mg three times daily for the treatment of acute flares of gout. Rheumatology (Oxford) 2007; 46:1126-32.
32. Li-Yu J, Clayburne G, Sieck M, Beutler A, et al. Treatment of Chronic Gout. Can we determine when urate stores are depleted enough to prevent attacks of gout. J Rheumatol 2001; 28:577-80.
33. Shoji A, Yamanaka H, Kamatani N. A retrospective study of the relationship between serum level and recurrent attacks of gouty arthritis: evidence for reduction of recurrent gouty arthritis with antihyperuricemic therapy. Arthritis Rheum 2004; 51:321-5.
34. Kramer et al. The association between gout and nephrolithiasis: The NNHeS III, 1988-1994. American Journal of Kidney Diseases 2002; 40:37-42.
35. Perez Ruiz F, Calabozo M, Pijoan JI, Herrero Beites AM, et al. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum 2002; 47:356-60.
36. Sarawate CA, Patel PA, Schumacher HR, Yang W et al. Serum urate levels and gout flares. Analysis from managed care data. J Clin Rheumatol 2006;12:61-65.
37. Bellamy N, Gilbert JR, Brooks PM, Emmerson BT, et al. A survey of current prescribing practices of anti-inflammatory and urate-lowering drugs in gouty arthritis in the province of Ontario. J Rheumatol 1988; 15:1841-71.
38. Ferraz MB, O'Brien B. A cost-effectiveness analysis of urate-lowering drugs in nontophaceous recurrent gouty arthritis. J Rheumatol 1995; 22:908-14.
39. Gibson T, Rodgers V, Potter C, Simmonds HA. Allopurinol treatment and its effect on renal in gout: a controlled study. Ann Rheum Dis 1982; 41:59-65.
40. Becker MA, Schumacher HR, Wortmann RL, MacDonald PA, et al. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. N Engl J Med 2005; 353:2450-61.
41. van Lieshout-Zuidema MF, Breedveld FC. Withdrawal of long term antihyperuricemic therapy in tophaceous gout. J Rheumatol 1993;20:1383-1385.
42. Bull PW, Scott JT. Intermittent control of hyperuricemia in the treatment of gout. J Rheumatol 1989; 16:1246-8.
43. Perez Ruiz F, Atxotegi J, Hernando I, Calabozo M, et al. Using serum urate levels to determine the period free of gouty symptoms after withdrawal of long-term urate-lowering therapy: a prospective study. Arthritis Rheum 2006; 55:786-90.