Asymptomatic hyperuricemia: which patient should be treated?: a review

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Abstract

Background: Patients with Asymptomatic Hyperuricemia (AHU) are often unnecessarily and almost systematically treated with Urate-Lowering Therapy (ULT), risking severe and sometimes fatal adverse effects. While symptomatic HU is almost always easily diagnosed and treated, ULT in AHU remains controversial. We performed a literature review to determine which patient should be treated, in light of the lack of consensus guideline. In fact, recommendations are still controversial regarding indications of ULT in asymptomatic hyperuricemia patients. Relevant databases were searched, and eligible trials were assessed.
Objective: The aim of this review was to present data on when ULT treatment should be initiated.
Data source: A literature search in Pub Med.
Results: Current research remains controversial. While non-pharmacological therapy with diet restriction and exercise is recommended for all patients with AHU, further studies identifying guideline for the ULT for AHU would be beneficial. However, some practical key points are to consider: ULT is not likely to slow Chronic Kidney Disease (CKD). Consequently, patients with better preserved renal function and children, might benefit more from an early ULT. However, more studies are needed to investigate if ULT decelerates GFR decline and progression to CKD (especially Stages III-V) and if patients with CKD benefit from ULT. Maintain lifelong serum uric acid levels lower than 6mg/dL for patients at high cardiovascular risk and the target level should be 5mg/dL. Allopurinol is recommended as a first-line ULT. To this end, we propose a practical algorithm for the management of AHU and hope that our work will be useful in making therapeutic decision.

Key words: Asymptomatic hyperuricemia, Crystals depositions, Joint ultrasound, Comorbidities, Therapeutic approach, Allopurinol

Introduction

Uric acid is a weak organic acid, the end product of purine nucleotides degradation[1]. It is known as the major antioxidant agent in human plasma. However, its antioxidant nature comes to its own opposite within the cell, where it paradoxically converts to a pro-oxidant agent, which mostly targets lipids (LDL and membranes)[2]. Its concentration is controlled by synthesis and cell turnover and, on the other hand, by the rate of destruction, excretion, and reabsorption by the kidney[3]. Hyperuricemia is a common metabolic disorder. It occurs when inherited or acquired conditions decrease the ability of the kidneys to secrete uric acid, since more than 70% is excreted by the kidneys[4]. It has a male dominance. In women, the incidence increases in postmeopause. It can be diagnosed by the level of Serum Uric Acid (SUA) above 420µM (70µg/ml). AHU is defined as an abnormally high serum urate level, without gouty arthritis or nephrolithiasis[5]. It leads to widespread uric acid deposition in a variety of tissues. The first clinical presentation of hyperuricemia is the development of gouty arthritis. If left untreated, crystal deposition can occur in multiple joints, and generate a significant inflammatory response[6]. On the other hand, experimental studies show that MSU crystals can also deposit in blood vessel walls, which could lead to many cardiovascular diseases such as arterial hypertension, stroke, and heart diseases[7,8], and in the kidneys, resulting in a chronic kidney disease[9]. If the clinical significance of hyperuricemia as a risk factor for vascular events remains unresolved, this will lead to ambiguity regarding the need to treat asymptomatic hyperuricemia[10,11]. For the rheumatologist, the use of ultrasound to detect early crystal deposits on joints in subjects with asymptomatic hyperuricemia may help to make a good therapeutic decision in a complex situation.

Materials and methods

In this narrative review, we performed a literature search in PubMed on articles published in English between January 2001 and September 2021, using the term " asymptomatic hyperuricemia treatment" in combination with (AND) "chronic kidney disease", "metabolic syndrome", "cardiovascular disease", and "ultrasonography". In addition, we searched websites of guideline-producing organizations, including the American College of Rheumatology and the Japanese Society of Gout and Nucleic Acid Metabolism. More than 400 articles were found, and we chose the most relevant ones according to their titles. Articles relevant to these searches were also identified in the authors' personal files.

Results

Asymptomatic hyperuricemia (AHU) is a very common condition in daily practice, evaluated by different specialties, mainly nephrology, cardiology, and rheumatology. We will respectively review the viewpoints of these specialties, then we will suggest a practical algorithm for the management of AHU and hope that our work will be useful in making therapeutic decisions. We identified a total of 435 articles. These articles were reviewed for relevance to the topic. A total of 27 studies were included in this review, among which 10 meta-analysis, 5 societies' guidelines and recommendations, and 2 systematic reviews. We focused on articles on the management of AHU and excluded articles on symptomatic hyperuricemia. In Africa, the lack of local guidelines due to the scarcity of epidemiological and therapeutic data make it difficult to make recommendations on gout or the management of hyperuricemia with specific regard to the African continent. More detailed information on gout in Africa could be found in a study by Genga *et al*[12] and other studies[13-16].

Hyperuricemia and renal diseases

It is now well established and there is increasing evidence, based on both experimental and epidemiological findings, that hyperuricemia represents a risk factor for the development and progression of CKD[17-23]. The relationship between hyperuricemia (HU) and chronic kidney damage is bidirectional. Although a reduction in Glomerular Filtration Rate (GFR) can precede and lead to the development of hyperuricemia, increased SUA levels can negatively impact renal function[24–25]. Several epidemiological studies suggest that elevated uric acid is strongly associated with the development of CKD but not universally with the progression of CKD. In a recent meta-analysis involving 13 observational trials with more than 190,000 patients with normal renal function, the presence of hyperuricemia was an independent predictor of the development of CKD. In hyperuricemia, the risk of new-onset CKD was twofold increased, and this effect was seen with comparable magnitude in both patients with and without diabetes[26]. These findings establish a firm association between hyperuricemia and the development of nephropathy in healthy subjects. However, evidence for secondary prophylaxis (i.e., prophylaxis for progression) in patients with CKD still remains debatable. Certain epidemiological studies showed no relationship between hyperuricemia and the progression of kidney disease[27,28]. Whether ULT retards the progression of CKD is still seriously controversial. While previous small-controlled clinical studies suggested a positive effect[29], recent trials on the role of allopurinol in preventing CKD progression did not confirm any favourable effect. Two large, randomized-controlled clinical trials, recently published in the *New England Journal of Medicine*, confirmed these findings. The PERL trial (Preventing Early Renal Loss in Diabetes) looked at the effect of allopurinol on preventing glomerular filtration decline in type 1 diabetes patients with mild to moderate diabetic nephropathy[30]. The CKD-FIX trial, which included both diabetic and non-diabetic patients, evaluated the effect of the inhibition of xanthine oxidase on the progression of kidney disease in patients with CKD, a lower baseline glomerular filtration rate, and a high risk of progression[31]. Both studies did not confirm a favourable effect of allopurinol on the evolution of kidney disease, but they had several limitations. Chen Qi *et al*[32] found that ULT was associated with the reduction of blood pressure and retardation of the decline in GFR overtime. The authors did not find benefits in clinical outcomes, including major adverse CV events, all-cause mortality, and kidney failure, but results were conditioned by short follow-up or low quality of the trials[32]. In summary, the nephroprotective role of ULT is still not confirmed; further trials may demonstrate its beneficial effect. Moreover, ULT is not likely to slow CKD. Therefore, patients with better preserved renal function and children might benefit more from an early ULT.

Hyperuricemia and cardiovascular diseases

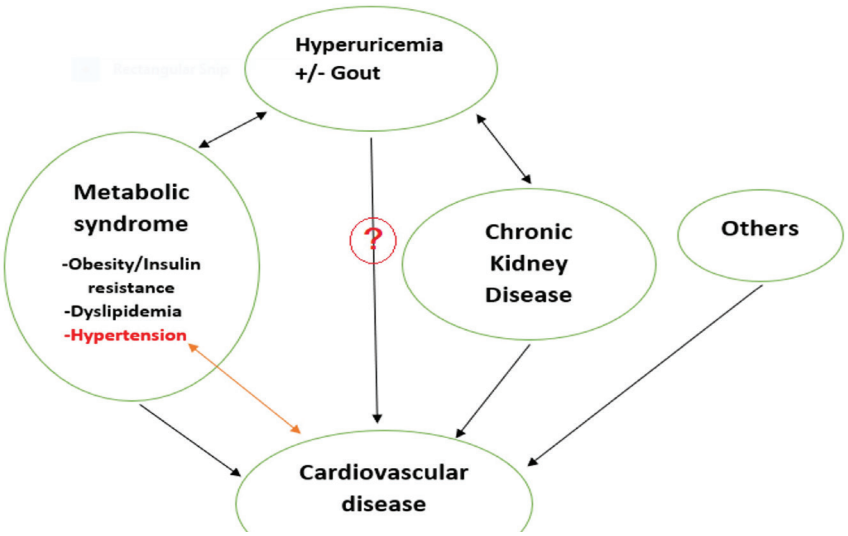
Over the last 20 years, the association of hyperuricemia with cardiovascular diseases has been re-examined following the demonstration in animal models that hyperuricemia could cause vascular disease[33-35]. Aside from its known antioxidant effect, strictly extracellular, soluble intracellular uric acid appears to cause significant endothelial and vascular disorders. Several mechanisms were suggested to explain its role, such as activation of the renin-angiotensin system, stimulation of smooth muscle cell proliferation, reduced nitric oxide synthase activity, and increased insulin resistance[36]. Furthermore, more recent evidence suggests that HU is linked to arterial obstruction by increasing plaque fragility in connection to hyperlipidaemia and decreasing fibrous volume[37,38]. In one study on coronary arteries obtained from 55 explanted hearts, monosodium urate crystal deposition was found in 6 cases[39], suggesting their role in the high rate of cardiovascular death[40], coronary heart disease[41],

heart failure, atrial fibrillation[42], stroke[43], and leading to refractory hypertension. Some authors suggest a role also for xanthine oxidase, which is responsible for oxidative processes[44], that themselves have an independent effect on CVD by endothelial dysfunction. Thus, in the case of xanthine oxidase inhibitor treatment, allopurinol improves endothelial function by profoundly reducing vascular oxidative stress and not by lowering UA[44]. Aside from this potential causal relationship between SUA and CVD, other authors[45], have reported a link between hyperuricemia and some known cardiovascular risk factors[45]. We look forward to the results of the ALL-HEART study, which is an ongoing multicentre, controlled, prospective, randomized trial examining the effects of allopurinol (up to 600mg daily) vs. no treatment on cardiovascular outcomes in patients with coronary artery disease. The secondary goals are to determine the cost-effectiveness of adding allopurinol to usual therapy, whether allopurinol improves quality of life, and to determine the safety and tolerability of giving allopurinol to patients with ischemic heart disease (without a history of gout)[46]. Several studies have confirmed the relationship between SUA and CVD mortality[47,48]. However, in their analysis, Rahimi-Sakak *et al*[48], found that the association between SUA level and CVD mortality risk, although positive in pooled results (HR 1.45, 95% CI 1.33–1.58, I2 = 79%), was stronger in women than in men. In addition, there was a significant non-linear association between them (r = 0.0709, p = 0.001). The Japanese Guideline on the Management of Asymptomatic Hyperuricemia (JGMHG), 3rd edition recommends pharmacological treatment of hyperuricemia in patients with CKD, emphasizing the importance of the cardio-renal continuum for treatment of asymptomatic hyperuricemia patients with hypertension and heart failure[49]. Recently, an updated management strategy with five-step recommendations for the treatment of 140 patients with increased SUA levels has been developed as illustrated in Figure 1. Finally, the definite answer to the difficult problems of independence of UA in relation to cardiovascular risk, especially the causality and reversibility issues, could not be obtained without a positive therapeutic trial. Cooperation between cardiologists, nephrologists, and rheumatologists is crucial in ULT trials.

Rheumatology's viewpoint on AHU: Gout is a systemic disease that results from the deposition of MSU in tissues. The clinical picture of gout includes asymptomatic hyperuricemia, acute gouty arthritis, the inter-crisis period, and chronic tophaceous gout[50]. The gold standard for its diagnosis is the visualization by optic microscopy of crystals in synovial fluid[51-53]. One study found that almost 10% of adults are documented to have hyperuricemia at least once in their lifetime, but only 22% of people with extremely high levels of SUA (more than 535mol/L, e.g., 8,9 mg/dL) will develop symptomatic gout during the five-year period of follow-up[54].

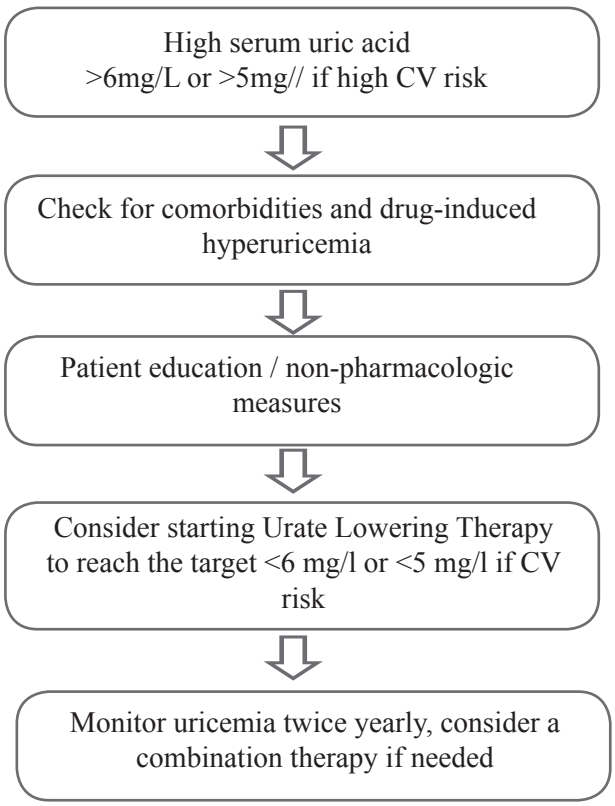
A prediction tool for incident gout among those with hyperuricemia: Siemons *et al*[54] developed an easy-to-use prediction tool for identifying patients with asymptomatic hyperuricemia at high risk for developing gout. The tool was developed using the risk factors of known gout, such as high blood pressure, diabetes, kidney failure, diuretics, obesity, and alcohol consumption, but also other factors such as age, gender, ethnicity, anaemia, blood lead, etc. The resulting simplified prediction tool (Figure 2) discriminated well between patients from different risk strata. If the score is 8 or less, the risk of gout is low. If it is 18 or more, the risk is high. If low-risk patients are considered to be the reference, the risk of incidental gout is 1.77 (CI95: 1.57–1.99) and 3.75 (CI95: 3.13–4.48) for patients at moderate and high risk, respectively. The odds ratios of prevalent gout are 3.37 (95% CI: 2.17–5.20) and 4.38 (CI95: 1.50–24.93) for patients at moderate and high risk, respectively. This easy-to-use score may allow us to assess the risk of gout in a population with hyperuricemia. It's stays to be validated prospectively

Figure 1: Illustrates the relationship between recognized CV risk variables and hyperuricemia, highlighting the challenges in establishing a direct causal link between hyperuricemia and CVD. (Shah, 2017)



in asymptomatic populations, where it will have its full place if its metrological properties are confirmed.

Figure 2: Illustrates a s-step strategy for the management of hyperuricemia; CV -cardiovascular (Borghi, *et al.* 2021[15])



Association of three genetic loci with uric acid concentration and risk of gout: Dehghan *et al*[55] identified three genetic loci (SLC2A9, ABCG2, and SLC17A3). Gout is associated with uric acid concentration and gout. A score based upon genes with a putative role in renal urate handling showed a substantial risk for gout.

Ultrasonography's role in early gout diagnosis: Ultrasonography (US) might appear as a useful tool in the management of this disease. In gout, two US features are quite specific and might be pathognomonic: the double contour sign and aggregates evocative of tophus[56–59]; Furthermore, MSU crystal deposition can be seen in ultrasound (US) images not only in inflamed joints but also in joints that have never been affected by overt arthritis[60]. The sensitivity of the ultrasound urate tissue deposition finding (double contour sign or tophus) is variable and ranges from 20% to 90%, which depends on previous therapy, data availability, study type (prospective or retrospective), type of observed joints, etc. The specificity is 98-100%. The most acceptable balance of sensitivity and specificity was reached by Naredo *et al*[61]. US examination standard recommendation[61], which demands evaluation of 6 anatomic structures bilaterally and simultaneously (12 regions): 3 structures for Tophus hyperechoic aggregates: 1 joint-radiocarpal and 2 tendons-patellar ligament and the triceps muscle tendon and 3 cartilages for the double contour sign: first metatarsophalangeal joint, second metacarpophalangeal joint, and calcaneal or femoral condyle cartilage. The sensitivity of Naredo's examination is 85%, specificity 83%, positive predictive value 92%, and negative predictive value 71%[62]. In light of this data, we can consider that US might be a valuable tool to identify hyperuricemia patients at risk for gouty arthritis. Dual energy CT and MRI could be used for the detection of MSU crystal deposits and tophi. However, ultrasound remains the cheapest and most convenient tool.

In summary, if for gout management, strong recommendations have been generated by international specialty societies, it is still controversial for AHU individuals. Currently, there is still considerable disagreement with regard to whether AHU should be treated,[62–64], probably due to the fact that both low and high SUA levels are associated with a high all-cause and cause-specific mortality rate with a U-shaped relationship[65,66]. Furthermore, a very low SUA level has some adverse effects, such as paradoxical arterial hypertension and increased dementia risk.

Figure 3: scoring chart for determining a patient's risk for developing gout. The risk is rated as low, moderate or high. (Siemons, *et al,* 2012[54])

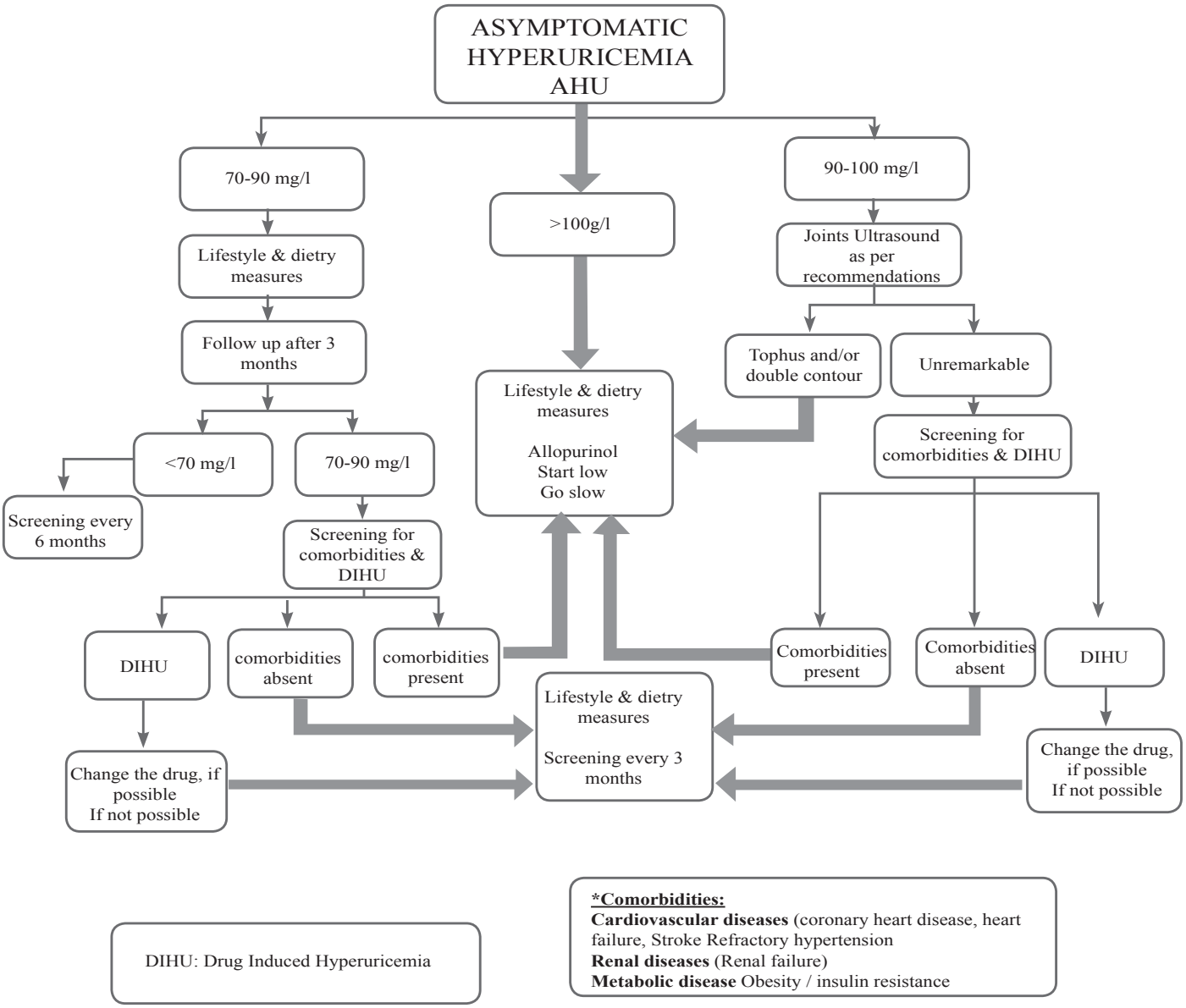
Patient's risk for gout
Start with a risk of 0

If:		Risk score
Age: < 45		+0
Age: 46-52		+1
Age: >53		+2
Body mass index: <25		+0
Body mass index: 25 - 29.99		+4
Body mass index: 30 - 34.99		+7
Body mass index: > 35		+9
Chronic kidney disease:	No	+0
Chronic kidney disease:		+2
Diabetes mellitus:	No	+0
Diabetes mellitus:	Yes	+3
Diuretic use:	No	+0
Diuretic use:	Yes	+6
Total score		0 - 25
If total score: 0 - 8		Low risk
If total score: 9 - 17		Moderate risk
If total score: 18 - 25		High risk

According to the American College of Rheumatology Guidelines 2020 for the Management of Gout, ULT is conditionally recommended even in patients with comorbidities and MSU crystal deposition as seen on imaging[67], which is consistent with Australian and New Zealand recommendations[68]. Conversely, the Japanese Guideline on the Management of Asymptomatic Hyperuricemia (JGMHG), 3rd edition, recommends pharmacological treatment of hyperuricemia in patients

with CKD, emphasizing the importance of the cardio-renal continuum for treatment of asymptomatic hyperuricemia patients with hypertension and heart failure. In order to reduce mortality in hyperuricemic patients with either hypertension or heart failure, ULAs could be used, when patients agree[68]. To sum up, given the lack of an international consensus on the management of AHU and based on the current data, we proposed an algorithm for the management of AHU taking into account uric acid level, joints ultrasound findings, and comorbidities (Figure 4).

Figure 4: Our proposed AHU therapeutic decision algorithm. Taking into account comorbidities, joints ultrasound findings, concomitant drugs, and SUA level



Conclusions

Current research on AHU management remains controversial. While non-pharmacological therapy with diet restriction and exercise is recommended for all patients with asymptomatic hyperuricemia, further studies identifying guidelines for the ULT in AHU would be beneficial. Patients with better preserved renal function and children might benefit more from an early ULT. However, more studies are needed to investigate if ULT decelerates GFR decline and progression to CKD (especially Stages III–V) and if patients with CKD benefit from ULT. Patients with comorbid CKD, CVD, urolithiasis, or hypertension, as well as those with asymptomatic hyperuricemia and MSU crystal deposition on imaging, which some authors consider to be pre-clinical gout, could be a candidate target group for prophylactic ULT, on which future research should focus. To this end, we proposed a practical algorithm for the management of AHU and hope that our work will be helpful in making therapeutic decisions. But our proposed algorithm should be evaluated in prospective studies.

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