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Indonesian Rheumatology Association (IRA) Recommendations for Diagnosis and Management of Hyperuricemia and Gouty Arthritis

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A B S T R A C T

Background: Gout is a progressive systemic disease caused by deposition of monosodium urate (MSU) crystals in various tissues such as joints, kidneys, and other connective tissues as a result of chronic hyperuricemia. If this condition is not adequately treated, it may progress to chronic gout, tophus formation, and even serious kidney function problems, which will lower quality of life. With the emergence of new treatment options in the last several years, a better understanding of diagnosis and management is required by every physician in Indonesia.

Methods: A panel of eighteen selected rheumatologists from the Indonesian Rheumatologist Association (IRA) developed recommendations based on key questions formulated by a steering committee from IRA. These recommendation materials were taken from several online databases such as PubMed, Science Direct, and Google Scholar. Level of evidence and grades of recommendation were then assigned, and each member of the panellist team will assign a score to express their level of agreement.

Results: A total of 16 recommendations discussing the diagnosis, non-pharmacological and pharmacological therapies, as well as monitoring for hyperuricemia and gouty arthritis were formulated.

Conclusion: These recommendations can be used to help clinicians in accurately diagnosing hyperuricemia and gouty arthritis and choosing the most suitable therapy for their patients. All recommendation statements were tailored to the clinical setting, facility, and drug availability in Indonesia.

1. Introduction

Gout is a progressive systemic disease caused by the deposition of monosodium urate (MSU) crystals in various tissues such as joints, kidneys, and other connective tissues as a result of chronic hyperuricemia.[1] Without effective treatment, this condition can develop into chronic, tophus formation, and can even result in severe kidney dysfunction and decreased quality of life. Gouty arthritis affects 1-4% of the general population worldwide. The prevalence of gouty arthritis in men is 3-6% and women is 1-2% in western countries, while in Asia it is 4.4-8.8% in men and 1.3-3.6% in women. Based on these data, gouty arthritis is the most common inflammatory arthritis case in men.[1,2] The prevalence of gouty arthritis increases with age with an average of 7% in men aged >75 years and 3% in women aged >85 years.[3] The prevalence of gouty arthritis in Indonesia has never been studied, but the prevalence of hyperuricemia in Indonesia is 18.6-47.6%.[4] One study in West Java Indonesia on 173 respondents showed that 45.7% experienced increased serum uric acid levels accompanied by joint pain.[5]

Several studies have shown that the management of gouty arthritis is still not optimal, as indicated by the 57% inaccuracy in diagnosis, which results in inaccuracy in treatment.[6] The majority of these incidents are found in primary care, this is due to the absence of guidelines for the diagnosis and management of gouty arthritis.[7]

The Indonesian Rheumatology Association (IRA), whose members are heavily involved in research and services for gouty arthritis patients, considers it necessary to develop guidelines for the care of gouty arthritis in Indonesia by developing guidelines for the diagnosis and management of hyperuricemia and gouty arthritis. IRA 2018 gout recommendation was already out of date and needed to be updated.

2. Methods

The Indonesian Rheumatologist Association (IRA) formed a recommendation team to formulate recommendation questions for diagnosis dan therapy of hyperuricemia and gouty arthritis. There was also a team of supervisors (steering committee) consisting of rheumatologists from various branches of IRA and institutions in Indonesia, with at least five years of working experience as a rheumatologist. Each member of the panellist team gave an independent opinion regarding the level and strength of recommendations put forth by the recommendation team. No delegation from the pharmacy industry was involved in the process of developing these recommendations.

A total of 16 key questions were formulated to determine the recommendations for diagnosing and managing hyperuricemia and gouty arthritis in Indonesia: 1) How is the diagnosis of gout established?

2) What are the general principles involved in the management of hyperuricemia and gouty arthritis? 3) What are the general principles for evaluating patients presenting with hyperuricemia and gouty arthritis? 4) How should therapy be administered to effectively reduce serum uric acid levels in patients with asymptomatic hyperuricemia? 5) What are the proper methods for administering colchicine, NSAID monotherapy, or corticosteroids during acute attacks of gouty arthritis? 6) What is the recommended approach for administering combination therapy involving colchicine with NSAIDs or corticosteroids in the management of acute gouty arthritis? 7) How should anti-IL1 therapy be administered during acute attacks of gouty arthritis? 8) How should adrenocorticotropic hormone (ACTH) therapy be administered to patients experiencing acute gouty arthritis? 9) What are the guidelines for administering therapy aimed at reducing serum uric acid levels in patients with acute gouty arthritis? 10) How should prophylactic therapy for acute gouty arthritis be administered to patients in the intercritical phase of gout? 11) What are the recommended protocols for administering therapy to lower serum uric acid levels in patients with chronic gouty arthritis? 12) What is the target serum uric acid level recommended for patients with chronic gouty arthritis? 13) How should prophylactic therapy be administered to patients with chronic gouty arthritis? 14) What are the recommended treatment strategies for patients with gouty arthritis who also have comorbid heart disease? 15) How should gouty arthritis be managed in patients with comorbidities such as diabetes mellitus, hypertension, and dyslipidaemia? 16) What are the appropriate treatment approaches for gouty arthritis in patients with comorbid chronic kidney disease?

Literature search was conducted through online databases, including PubMed, Science Direct, Google Scholar, and other databases, using these keywords: hyperuricemia, gouty arthritis, diagnosis, gout attack, chronic gout, laboratory test, education, treatment, algorithm, monitoring, complication, and prognosis. The search was limited to published English meta-analysis, systematic review, clinical trial, randomized controlled trial (RCT), and observational study, published within 2018 to 2024. Initial literature search yielded 471 relevant articles. After a thorough reading, the team selected 93 articles to be included in the formulation of this recommendation.

The development of this diagnostic and management guideline is based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, which requires panellist team members were asked to rate each adaptation of scientific evidence summaries from existing clinical practice guidelines, if available, or generating de novo summaries of scientific evidence if necessary. This process includes (1) identifying prioritized research questions through (population-intervention-comparison-outcome) PICO framework, (2) extracting, assessing, and synthesizing scientific evidence from existing clinical practice guidelines, meta-analyses, and systematic reviews of clinical trials or observational studies, (3) formulating summaries of scientific evidence, (4) voting on critical and important outcomes, (5) presenting scientific evidence to the panellist team, (6) formulating final recommendations, and (7) planning for dissemination, implementation, and updating.

Recommendations were issued based on the 16 key questions above. The recommendation team then assigned the level of evidence (LoE) and grades of recommendation (GoR) based on the criteria listed in Table 1.11 These recommendations were then reviewed by the steering committee. In the final step, the recommendation on a scale of 0 to 10 to determine the level of agreement (LoA). A score of 0 indicated complete disagreement and 10 indicated complete agreement. The panellist member would be asked for comments should a score below 8 was issued. Recommendations with an average score below 8 were then rediscussed by the recommendation team to be revised and then reassessed by the panelist team to determine the final LoA.

Levels of evidence is a hierarchical system for classifying evidence based on the quality of the

methodological design, validity, and its applicability to patient care. On the other hand, grades of recommendation are based on levels of evidence, considering the overall strength of evidence and the judgment of recommendation makers. Grades of recommendation are developed by considering cost, value, preferences, feasibility, risk-benefit assessment, along with the assessment of the quality of available scientific evidence.

3. Results

Based on the discussion, 16 recommendations were agreed upon by the recommendation team, steering committee, and the panelist team. Summary of these recommendations can be seen in Table 2.

Table 1. Level of Evidence and Grades of Recommendations

Level of evidence (LoE)		Grades of recommendation (GoR)	
I	High quality meta-analysis or systematic review of RCTs, or individual RCTs with low risk of bias	A	Strong recommendation: referring to level I studies
II	High review quality of systematic observational studies (case control or cohort), or individual observational studies	B	Moderate recommendation: referring to level II studies or extrapolation of level I studies
III	Non-analytic studies (case report or case series)	C	Weak recommendation: referring to level III studies or extrapolation of level II studies
IV	Non-analytic low quality studies (case report or case series)	D	Consensus recommendation: expert opinion or based on limited evidence

Table 2. Summary of Recommendations for Diagnosis and Management of hyperuricemia and gouty arthritis

No	Recommendation	LoE	GoR	LoA
1.	The 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for gout are recommended for establishing the diagnosis of gouty arthritis.	I	A	9.48
2.	Every patient with hyperuricemia and gouty arthritis should receive adequate education about the condition, including lifestyle modifications such as maintaining an ideal body weight, limiting the consumption of certain purine-rich foods, engaging in regular physical exercise, and following an effective management plan for comorbid diseases.	I	A	9.47
3.	Every patient with gouty arthritis should undergo a systematic anamnesis and screening evaluation to identify comorbid diseases, particularly those that may influence therapy, such as impaired kidney function, coronary heart disease, heart failure, stroke, peripheral artery disease, obesity, hypertension, and diabetes.	I	A	9.69
4.	Patients with asymptomatic hyperuricemia are not currently recommended to receive serum uric acid-lowering therapy, except in specific circumstances.	I-II	B-C	9.40
5.	Monotherapy with colchicine, NSAIDs, or corticosteroids is recommended for the management of acute gout attacks.	I	A-B	9.25
6.	Combination therapy involving colchicine and NSAIDs or colchicine and corticosteroids is recommended for the management of acute gout attacks with polyarthritis or in cases where monotherapy proves ineffective.	I	A-B	9.63
7.	Anti IL-1 is recommended in certain conditions for acute gout attacks.	I	B	8.81
8.	Adrenocorticotropic hormone (ACTH) is not currently recommended for the treatment of acute gout attacks.	II	B	9.10
9.	Serum uric acid-lowering therapy is recommended to be initiated and maintained both during acute attacks and in periods of remission, with the goal of achieving and sustaining a target serum uric acid level of <6 mg/dL	I	A	9.33
10.	Prophylactic therapy with low-dose colchicine, low-dose NSAIDs, or low-dose corticosteroids is recommended at the initiation of serum uric acid-lowering therapy.	I	A	9.42

11.	Serum uric acid-lowering therapy is recommended for patients with chronic gouty arthritis, with or without tophi.	I	A	9.63
12.	A target serum uric acid level of <5 mg/dL is recommended for patients with chronic gouty arthritis.	I	A	9.47
13.	Prophylactic therapy for acute gout attacks is recommended for patients with chronic gouty arthritis who are receiving serum uric acid-lowering medications.	I	A	9.40
14.	The selection of serum uric acid-lowering therapy for patients with gouty arthritis and comorbid cardiovascular disease is recommended to be consistent with that for patients without cardiovascular comorbidities.	I-II	A-B	9.06
15.	Gouty arthritis patient with comorbidities such as diabetes mellitus, hypertension, and dyslipidaemia, it is recommended to choose medications that offer additional benefits in reducing serum uric acid levels.	I-II	A-B	9.54
16.	Gouty arthritis patients with chronic kidney disease (CKD), it is recommended to administer serum uric acid-lowering medications with dose adjustments at the initiation of therapy.	I	A-B	9.63

4. Discussion

Recommendation 1: The 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) classification criteria for gout are recommended for establishing the diagnosis of gouty arthritis

The natural history of gout consists of four phases, namely a) asymptomatic hyperuricemia, b) acute gouty arthritis, c) intercritical phase or phase interspersed with intervals without clinical symptoms, and d) chronic gout.[1] Diagnosis of acute, intercritical or chronic gouty arthritis can be done using the gout classification criteria according to the 2015 American College of Rheumatology/European League against Rheumatism (ACR/EULAR).[8]

Recommendation 2: Every patient with hyperuricemia and gouty arthritis should receive adequate education about the condition, including lifestyle modifications such as maintaining an ideal body weight, limiting the consumption of certain purine-rich foods, engaging in regular physical exercise, and following an effective management plan for comorbid diseases

Education with an interactive and patient-centered approach can improve patient knowledge of hyperuricemia and gouty arthritis. Optimal education will address gaps in knowledge, race, gender, socioeconomic status, and level of social support. Education can be provided in person, in writing, or via online media delivered individually or in groups.[9,10] The 2020 ACR guidelines recommend limiting alcohol, purine-containing foods, and high-fructose corn syrup in patients with gouty arthritis.[11] The 2021 Asia Pacific League of Associations for Rheumatology (APLAR) guidelines recommend reducing alcohol consumption to prevent gouty arthritis attacks or lower serum uric acid levels, while there is limited scientific evidence for consumption of high-purine foods to prevent gouty arthritis attacks or lower serum uric acid levels.[9]

The recommended sport is moderate aerobic exercise because it shows results in a decrease in serum uric acid in serum compared to heavy exercise which can temporarily increase serum uric acid levels. The study results showed that every increase in body mass index (BMI) increased the risk of gouty arthritis in each patient (Odd ratio [OR] 2.83; 95% CI 2.17-3.67), although BMI was not associated with the incidence of gouty arthritis attacks (OR 0.61 CI 95% 0.32-1.16).[9,12]

Recommendation 3: Every patient with gouty arthritis should undergo a systematic anamnesis and screening evaluation to identify comorbid diseases, particularly those that may influence therapy, such as impaired kidney function, coronary heart disease, heart failure, stroke, peripheral artery disease, obesity, hypertension, and diabetes

The 2022 National Institute for Health and Care Excellence (NICE) guidelines for the management of

gouty arthritis state that a complete history and physical examination should be performed to assess the symptoms and signs of gouty arthritis. Symptoms and signs include sudden onset of severe pain (often overnight) with redness and swelling in one or both first metatarsophalangeal joints (MTP-1) or a tophi.[13] The 2015 ACR/EULAR gout classification criteria can be used as a basis for a history and physical examination to help establish a diagnosis of gout.8 Patients should also undergo a screening evaluation to look for comorbid conditions, especially those that may affect therapy, such as impaired kidney function, coronary heart disease, heart failure, stroke, peripheral artery disease, obesity, hypertension, and diabetes (more details in recommendations 14 to 16).

Recommendation 4: Patients with asymptomatic hyperuricemia are not currently recommended to receive serum uric acid-lowering therapy, except in specific circumstances

The 2021 APLAR guidelines also state that there is not yet a strong enough basis to recommend or oppose the administration of serum uric acid lowering therapy.[9] The 2011 Japanese guidelines are slightly different, because they quite firmly state the administration of serum uric acid lowering therapy in asymptomatic hyperuricemia patients with serum uric acid levels >8 mg/dl. According to the findings of a cohort research involving healthy male participants, people with serum urate levels above 8.0 mg/dL, especially 9.0 mg/dL, have a considerably increased chance of developing gouty arthritis in the future than people with lower serum urate levels.[14]

In this guideline, the team agreed that it could not yet recommend due to the limited scientific evidence for the giving of serum uric acid lowering therapy in hyperuricemia patients who do not have a history of acute gouty arthritis attacks or no complications due to hyperuricemia.

Patients with asymptomatic hyperuricemia should be considered for serum uric acid lowering therapy if they have serum uric acid levels >9 mg/dl accompanied by evidence of one of the following conditions, namely a double contour image on joint ultrasound examination, joint fluid examination containing monosodium urate crystals, evidence of urinary tract stones.

Recommendation 5: Monotherapy with colchicine, Non-steroid Anti Inflammatory Drugs (NSAIDs), or corticosteroids is recommended for the management of acute gout attacks

The results of the meta-analysis showed that low-dose colchicine (1.5-1.8 mg/dl) is an effective dose for patients with acute gouty arthritis compared to placebo (Risk Ratio (RR) 2.43; 95% CI 1.05-5.64). Low-dose colchicine compared to high-dose colchicine (4.5-4.8 mg/dl) has the same effectiveness in treating pain in patients with acute gouty arthritis (RR 0.87; 95% CI 0.56-1.36).[9,11] Low-dose colchicine has the same benefits and effectiveness as non-steroidal anti-inflammatory drugs (NSAIDs) (RR 0.97; 95% CI 0.82-1.15).[15] We recommend giving colchicine at a dose of 1 mg followed by a dose of 0.5 mg one hour later. Monotherapy using colchicine is recommended for patients experiencing acute gouty arthritis attacks with mild to moderate pain and involving ≤2 joints. Attacks with severe pain and involving multiple joints are recommended to use combination therapy.[38] Colchicine should not be given to patients with severe renal impairment and should also not be given to patients receiving P-glycoprotein and/or CYP3A4 inhibitor therapy such as cyclosporine or clarithromycin.[16]

The meta-analysis results showed that NSAIDs can relieve pain within 24 hours compared to placebo (RR 2.75; 95% CI 1.13-6.72). Both non-selective and selective have the same effectiveness in relieving pain, reducing inflammation, and improving joint function (MD 0.03; 95% CI (-0.07)-0.14; MD 0.08; (-0.07)-0.22; MD 0.04; (-0.17)-0.25), but side effects were higher in the non-selective NSAID group (RR 1.94; 95% CI 1.36-2.78).[17]

Corticosteroids and NSAIDs have similar efficacy in

treating acute gouty arthritis attacks (MD 0.15; 95% CI (-2.71) - 3.02), (MD 0.33; 95% CI 0.07-0.69), and (MD 0.21; 95% CI (-2.22)-1.8).[17] Corticosteroids and NSAIDs also have relatively similar safety profiles (RR 0.76; 95% CI 0.47-1.23) and (RR 0.09; 95% CI 0.01-1.67).[17, 18]

Recommendation 6: Combination therapy involving colchicine and NSAIDs or colchicine and corticosteroids is recommended for the management of acute gout attacks with polyarthritis or in cases where monotherapy proves ineffective

Combination therapy is recommended for patients experiencing moderate-severe acute gouty arthritis attacks with >2 joints or for patients with inadequate response (pain reduction <20% in 24 hours or <50% after 24 hours).[19,20] Some recommendations for combination therapy are colchicine with NSAIDs, colchicine with oral corticosteroids or intra-articular corticosteroids with all modalities.[20] The use of similar combination therapies is not recommended.[19]

Recommendation 7: Anti IL-1 is recommended in certain conditions for acute gout attacks

The results of a moderate-quality systematic review showed that anti-IL-1 therapy is safe and effective in treating acute gouty arthritis attacks and is an option for patients who are not able to use standard therapy.[21,22] The results of a meta-analysis comparing a single dose of rilonacept 320 mg injection with a maximum dose of indomethacin 50 mg three times a day for three days showed that rilonacept provided less pain relief with the same risk of side effects (MD -2.52; 95% CI (-0.29) - (-4.75) and (RR 1.19; 95% CI 0.75-1.88).[23]

The results of two meta-analyses showed that canakinumab injection was more effective in reducing pain compared to intra-articular triamcinolone injection (MD -14.59 mm; 95% CI [-19.42] [-9.77]) and (MD -10.57; 95% CI [-15.24]-[-5.9]).[23,24] Overall patient improvement was also better in the canakinumab injection group (RR 1.44; 95% CI 1.28-1.61) and (RR 1.37; 95% CI 1.16-1.61).[23,24] Canakinumab injection can be given as an option for acute gouty arthritis attacks in patients who have contraindications to standard therapy.[22] The cost of using canakinumab should be considered, which is 5000 times higher than triamcinolone injection.[23]

Anti-inflammatory drugs IL-1 was not yet available in Indonesia at the time the recommendations were drawn up.

Recommendation 8: Adrenocorticotropic hormone (ACTH) is not currently recommended for the treatment of acute gout attacks

Based on the results of one RCT showed that ACTH and betamethasone have the same effectiveness and safety in patients experiencing acute gouty arthritis attacks, but ACTH has lower side effects on the Hypothalamic Pituitary Adrenal (HPA) axis.[25] Until this recommendation was prepared, there had been no meta-analysis or systematic review supporting the benefits of ACTH therapy in gouty arthritis patients, so the drafting team considered that scientific evidence was still very limited.

Recommendation 9: Serum uric acid-lowering therapy is recommended to be initiated and maintained both during acute attacks and in periods of remission, with the goal of achieving and sustaining a target serum uric acid level of <6 mg/dL

The results of three meta-analyses showed that administration of serum uric acid lowering therapy during an attack did not worsen or increase the duration of pain (MD -0.42; 95% CI (-0.42)-1.78), and (MD 0.06; 95% CI (-0.13)-0.25). There was no significant difference in the duration of resolution, C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) (MD -1.14; 95% CI (-5.63)-3.36) and (MD -2.51; 95% CI (-5.46)-0.45).[26,27] In patients with acute gout who have never received serum uric acid lowering therapy, the IRA considers

that it can be recommended during acute gout attacks, this is in line with the APLAR gouty arthritis management guidelines.[9]

The initial dose of allopurinol is started at ≤100 mg/day, but in patients with chronic kidney disease stages 4-5 or glomerular filtration rate (GFR) value <30 ml/min/1.73 m2, it is started with an initial dose of ≤50 mg/dL. The dose is evaluated for 2-4 weeks, if the target serum uric acid level has not been achieved, the dose of allopurinol can be increased until the target serum uric acid level is achieved, the maximum dose is 800 mg/day. The initial dose of febuxostat is started at ≤40 mg/day and evaluated for 2-4 weeks, if the target serum uric acid level has not been achieved, the dose can be increased, the maximum dose is 120 mg/day. Febuxostat does not require dose adjustment in patients with chronic kidney disease.[11,28] Serum uric acid levels should be monitored and attempted to be <6 mg/dl. Except in patients with severe gout (there is a hat, chronic arthropathy, frequent gouty arthritis attacks even though serum uric acid levels are <6 mg/dl), the target serum uric acid level is attempted to be <5 mg/dl to dissolve monosodium urate crystals.[29,30]

Recommendation 10: Prophylactic therapy with low-dose colchicine, low-dose NSAIDs, or low-dose corticosteroids is recommended at the initiation of serum uric acid-lowering therapy

Prophylaxis of acute gouty arthritis attacks in patients receiving serum uric acid-lowering therapy is given for 3-6 months from the start of serum uric acid-lowering therapy, with low-dose colchicine (0.5-1 mg/day). Colchicine has been shown to reduce the frequency and severity of acute gouty arthritis attacks and does not increase the incidence of side effects such as the risk of cancer, sepsis, cytopenia, and myotoxicity.[31] Administration of colchicine for up to six months along with serum uric acid-lowering therapy has been shown to be well tolerated.[4]

Non-steroidal anti-inflammatory drugs or corticosteroids can be an alternative in patients who are intolerant or contraindicated to colchicine.[9,11,32] low-dose NSAIDs (e.g. naproxen 2x250 mg) in patients who are intolerant or contraindicated to colchicine. Giving small doses of NSAIDs such as naproxen 2x250 mg or etoricoxib 1x60 mg has the same effectiveness as colchicine but the risk of side effects must be considered, especially with long-term use. Small doses of corticosteroids equivalent to 7.5 mg of prednisone can also be an alternative, although its effectiveness is not as good as colchicine.[33] Anti IL-1 can be an alternative in patients who cannot use colchicine, NSAIDs, and corticosteroids.[32] If there is an acute gouty arthritis attack in the middle of prophylactic therapy using colchicine, it is recommended to add other anti-inflammatories such as NSAIDs or corticosteroids.

Recommendation 11: Serum uric acid-lowering therapy is recommended for patients with chronic gouty arthritis, with or without tophi

Uric acid lowering therapy is recommended for patients with chronic gouty arthritis to maintain serum uric acid levels, prevent attacks, and reduce complications due to hyperuricemia. The results of a meta-analysis of the use of uric acid lowering therapy in patients with chronic gouty arthritis have proven effective in maintaining serum uric acid levels, preventing attacks, and reducing complications due to hyperuricemia (RR 9.13; 95% CI 2.33-35.87) and improving patients' global quality of life (RR 1.83; 95% CI 1.05-3.19).[34]

The use of ULT is adjusted to the clinical conditions and contraindications in the patient. Patients with gouty arthritis who receive serum uric acid lowering therapy but have not reached the target, often experienced gouty arthritis attacks, and have tophus that do not improve despite using optimal xanthine oxidase inhibitor, uricosuric, or other interventions, can use pegloticase.[11]

Recommendation 12: A target serum uric acid level of <5 mg/dL is recommended for patients with

chronic gouty arthritis

The target serum uric acid level in patients with chronic gouty arthritis with or without tophi is <5 mg/dL to dissolve monosodium urate crystals.[11,13,35,36] Serum uric acid levels <3 mg/dL are not recommended in the long term because they are thought to cause neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and other motor disorders.[37,38] All drug options for lowering serum uric acid levels start at a low dose and the dose is titrated upward until the target serum uric acid level is achieved and maintained throughout life.[11] Administration of drugs to lower serum uric acid levels aims to reduce serum uric acid levels in the patient's serum. The 2022 NICE guidelines consider a target serum uric acid level of <5 mg/dL in gout patients who have chronic gouty arthritis or who have frequent attacks of acute gouty arthritis even if the serum uric acid level is <6 mg/dL.[13]

Recommendation 13: Prophylactic therapy for acute gout attacks is recommended for patients with chronic gouty arthritis who are receiving serum uric acid-lowering medications

Prophylaxis of acute gouty arthritis attacks in patients receiving serum uric acid lowering therapy is given for 3-6 months from the start of serum uric acid lowering therapy, with low-dose colchicine (0.5-1 mg/day) or low-dose NSAIDs in patients who are intolerant or contraindicated to colchicine.[9,11] If colchicine and NSAIDs are contraindicated, low-dose corticosteroids can be given.[39] Prophylaxis can be given for 3-6 months.[11]

The results of a meta-analysis showed that acute gouty arthritis attacks were lower in the group given prophylaxis 30.5% compared to the group without prophylaxis 55.9% (RR 0.36; 95% CI 0.27-0.48).[11] Colchicine combined with allopurinol or febuxostat has the same effectiveness in reducing the risk of acute gouty arthritis attacks (RR 0.48; 95% CI 0.32-0.74), while the risk of acute gouty arthritis attacks in the allopurinol group was lower compared to probenecid (0.4 vs 1.24 attacks per month, p<0.0001).[9]

Recommendation 14: The selection of serum uric acid-lowering therapy for patients with gouty arthritis and comorbid cardiovascular disease is recommended to be consistent with that for patients without cardiovascular comorbidities

The choice of serum uric acid lowering therapy in gouty arthritis patients with heart disease is still debated. The results of a meta-analysis indicate that administering allopurinol to gouty arthritis patients reduces the risk of cardiovascular side effects (RR 0.65; 95% CI 0.46-0.91; p=0.012) and the risk of myocardial infarction (RR 0.47; 95% CI 0.27-0.80; p=0.01) compared to the control group.[40] A meta-analysis concluded that the use of febuxostat compared to Allopurinol in the Asian population was associated with a significant increase in cardiovascular risk in patients with and without gout.[41] The results of a recent study differed in that febuxostat was not associated with an increased risk of cardiovascular complications (OR 0.93; 95% CI 0.75-1.15; p=0.52).[42] One of the international guidelines states that gouty arthritis patients with heart disease who receive febuxostat need to be replaced with other serum uric acid lowering therapy options, while the Asia-Pacific guidelines state that there is insufficient scientific evidence to recommend or oppose the use of serum uric acid lowering therapy in patients with gouty arthritis with heart disease.[9,11] Considering that the latest meta-analysis results have not yet provided consistent results, the IRA cannot yet recommend or oppose the administration of febuxostat as a serum uric acid lowering therapy option in patients with gouty arthritis with heart disease.

Recommendation 15: Gouty arthritis patient with comorbidities such as diabetes mellitus, hypertension, and dyslipidaemia, it is recommended to choose medications that offer additional benefits in reducing serum uric acid levels

RCT study showed that Sodium-Glucose Transport Protein-2 (SGLT-2) inhibitors have strong potential to reduce serum uric acid levels in patients with type 2 diabetes compared to other diabetes drugs, but if it is difficult to obtain SGLT-2 inhibitors or there are contraindications to the use of these drugs, allopurinol can be given.[43] The results of two meta-analyses showed that SGLT-2 inhibitors consistently reduced serum uric acid levels (WMD -37.73 µmol/ L, 95% CI [-40.51] - [34.95]) and (MD -34.07 µ mol /L, 95% CI [-37.00] - [31.14]).[44,45] The results of another meta-analysis showed that SGLT-2 inhibitors could be an option for patients with type 2 diabetes who are at high risk of gouty arthritis because they provide additional benefits.[45]

The choice of serum uric acid lowering therapy in patients with gouty arthritis and hypertension must be adjusted to the clinical condition of each patient, considering side effects and drug interactions. Allopurinol and febuxostat are the main choices, with losartan as an antihypertensive therapy agent that provides additional benefits in the management of both conditions. The results of the study showed that allopurinol and febuxostat have the same effectiveness in patients with gouty arthritis with hypertension. Losartan can lower blood pressure while lowering serum uric acid levels, so it is also called a uricosuric agent.[46,47]

Selection of serum uric acid lowering therapy in patients with gouty arthritis and dyslipidaemia based on meta-analysis showed that statins were significantly associated with decreased serum uric acid levels, especially atorvastatin, which was proven to be the most effective in lowering serum uric acid levels. Atorvastatin is the most appropriate cholesterol-lowering agent for patients with or at risk of hyperuricemia.[44]

Recommendation 16: Gouty arthritis patients with chronic kidney disease (CKD), it is recommended to administer serum uric acid-lowering medications with dose adjustments at the initiation of therapy

Determination of serum uric acid lowering therapy dose must consider creatinine clearance in gouty arthritis patients with chronic kidney disease. International guidelines state that xanthine oxidase inhibitors such as febuxostat are the first-line therapy of choice for gouty arthritis patients with chronic kidney disease at stage ≥3. Allopurinol administration can prevent worsening of kidney function in patients with or without chronic kidney disease.48 69% of gouty arthritis patients with CKD achieved the target serum uric acid and 59% of patients were able to maintain serum uric acid levels <6 mg/dL. Initial administration of allopurinol begins with a dose of ≤100 mg/day evaluated for 2-4 weeks, then the dose can be increased until the target serum uric acid is achieved, but in patients with chronic kidney disease stages 4-5 it is started with an initial dose of ≤50 mg/dL.[49]

Febuxostat has also been shown to slow the worsening of kidney function in patients with chronic kidney disease (WMD 2.69; 95% CI 1.07-4.31).50 The results of the meta-analysis showed that the group with febuxostat had a higher glomerular filtration rate and lower serum uric acid levels compared to the group with allopurinol or placebo (WMD 2.897, 95% CI: 1.336-4.458, p<0.001).[84,85] Another advantage of febuxostat is that it is safe in patients with chronic kidney disease stage 3-4 and does not require dose adjustment if creatinine clearance is >30 ml/minute.[50] Febuxostat has also been shown to be safe for use in patients with chronic kidney disease stage 4-5 who have not undergone dialysis.[51] Febuxostat is started at a low dose of ≤40 mg/day, but in CKD stage 4-5 it is started at a lower initial dose.[52]

5. Conclusion

These recommendations aim to provide guidance on the diagnosis and management of hyperuricemia and gouty arthritis in Indonesia. The diagnostic, therapy, and monitoring algorithms in this recommendation are all tailored to suit Indonesia's

clinical setting, facility, and drug availability.

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