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Medical Guidelines

Hyperuricemia: Clinical Practice Guidelines

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Hyperuricemia, linked to the rising prevalence of metabolic syndrome, obesity, ischemic heart disease, and chronic kidney disease, has become an alarming public health concern. It arises due to overproduction, underexcretion, or a combination of both processes involving uric acid. Defined as a plasma uric acid concentration exceeding 6.8 mg/dL (404.5 µmol/L), hyperuricemia is associated with conditions such as gout—a metabolic disease characterized by recurrent acute arthritis, urate deposits, and chronic joint deformities. Although hyperuricemia often remains asymptomatic, it plays a significant role in gout's development when serum uric acid exceeds the solubility threshold. However, chronic hyperuricemia is observed in many individuals without gout or uric acid stones.[1]

Prevalence: Globally, 10–40% of adults have hyperuricemia, with varying prevalence depending on comorbidities and geographical factors. In Pakistan, 30.1% of the Karachi population and 31.9% of Faisalabad's population are affected. Comorbid conditions like chronic kidney disease increase prevalence, with studies showing rates as high as 76.7% in dialysis patients. Gout predominantly affects men over 30 and postmenopausal women, with around 90% of cases involving males.[2]

Etiopathogenesis: Uric acid is the product of purine metabolism, primarily synthesized in the liver and excreted through the kidneys (two-thirds) and intestines (one-third). The solubility threshold is 6.4–6.8 mg/dL, with a heritable component contributing to primary gout. Genetic studies have linked gout risk to genes regulating renal urate handling. Secondary gout arises from acquired causes, including uric acid underexcretion, overproduction, or both.

Underexcretion: Causes include idiopathic factors, familial juvenile gouty nephropathy, kidney insufficiency, metabolic syndrome, certain drugs (e.g., diuretics, low-dose salicylates), hypertension, acidosis, preeclampsia, hypothyroidism, hyperparathyroidism, sarcoidosis, chronic lead intoxication, and genetic disorders such as Down syndrome.[3]

Overproduction: This can occur idiopathically or due to inherited disorders like Lesch-Nyhan syndrome and Kelley-Seegmiller syndrome. Other causes include increased PRPP synthetase activity, diets rich in purine-containing foods, elevated nucleic acid turnover (e.g., in malignancies), tumor lysis syndrome, glycogenoses, or exposure to organic pollutants.

Combined Causes: Alcohol, fructose consumption, exercise, diabetes, heart failure, and genetic conditions like aldolase B or glucose-6-phosphatase deficiencies contribute to both increased uric acid production and decreased renal excretion.

Clinical Manifestations: Patients may present asymptomatically or with symptoms of gout or nephrolithiasis.[4]

- ***Gout:*** Often begins with acute monoarthritis, commonly in the great toe (podagra). Chronic forms may evolve after repeated acute attacks, resulting in polyarthritis and deformities mimicking rheumatoid arthritis.
- ***Nephrolithiasis:*** Uric acid kidney stones manifest as hematuria, flank pain, or nausea.

Hyperuricemia is also linked to cardiovascular risks, with patients facing a higher likelihood of coronary or cerebrovascular diseases.

Physical Examination: While many hyperuricemic patients are asymptomatic, acute gouty arthritis presents a swollen, erythematous, and warm joint, often accompanied by fever. Chronic gouty arthritis may involve tophi formation, and uric acid nephrolithiasis may cause abdominal tenderness.

Differential Diagnosis: Conditions like cellulitis, pseudogout (distinguished by calcium pyrophosphate crystals), rheumatoid arthritis, hemarthrosis, and tendinitis/ bursitis may mimic gout. Identifying urate crystals through fluid

analysis and imaging helps confirm the diagnosis.[4]

Investigations: Diagnosis involves serum uric acid levels, but a normal reading during acute gout flares does not exclude gout. Identifying urate crystals in joint fluid or tophi confirms the condition.

- ***Additional tests:*** CBC, renal function tests, liver function tests, glucose levels, lipid profiles, and imaging (ultrasonography or dual-energy CT) assess comorbidities and disease complications.
- ***24-hour urine analysis:*** Helps categorize patients into high-purine intake, overproducers, or underexcretors based on uric acid excretion levels. Spot urine uric acid-to-creatinine ratios are also useful when 24-hour collections are impractical.

Management

Non-Pharmacological Measures: Dietary modifications are crucial for managing hyperuricemia and gout prevention. Patients should adopt a low-purine diet, avoiding high-purine foods (meats, seafood, organ meats, alcohol), high-fructose corn syrup, and saturated fats.[5]

Pharmacological Interventions

- ***Acute Gout:*** NSAIDs are the first line, resolving attacks within 3–10 days. Colchicine and corticosteroids are alternatives in certain cases.
- ***Chronic Gout:*** Urate-lowering therapy (ULT) is initiated with medications like allopurinol or febuxostat. Probenecid is an option for underexcretors.
- ***Nephrolithiasis:*** Alkalinization of urine with potassium citrate or bicarbonate and hydration reduces stone formation.
- ***Weight:*** Maintain a healthy weight by keeping BMI within the normal range for the Asian population (18.5 to 22.9 kg/m²).
- ***Water:*** Aim to consume 8–10 glasses of water daily (unless contraindicated). A daily urinary output of 2 liters or more can help excrete urates and minimize urate precipitation in the kidneys.
- ***Dietary Recommendations:*** The Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet is beneficial for reducing serum uric acid concentrations. Focus on a balanced food intake, ensuring no more than two servings of protein daily. Choose low-fat dairy or plant-based protein sources like nuts, soy, eggs, or low-fat cheese. Include plenty of fruits and vegetables, aiming for five portions daily. Avoid foods high in purines when possible.[6]

Foods without restrictions include

- Bread, cereals (except whole grain), pasta, potatoes, and rice.
- Fruits, vegetables, and nuts.
- Low-fat dairy products, eggs.
- Fats and oils (reduce intake if overweight).
- Tea and coffee.
- *Dairy Products:* High consumption of dairy products has been associated with a lower risk of hyperuricemia.
- *Fiber:* Increase fiber intake to 25–30 grams daily.
- *Probiotics:* Probiotics may improve gut microflora balance, which is often disrupted in hyperuricemia. They may also help absorb purines and inhibit xanthine oxidase activity.
- *Alcohol:* Excessive alcohol consumption can trigger gout attacks and should be avoided.7

Purine Content of Common Foods

- Rice (1 cup cooked): 20–50 mg
- Noodles (1 cup cooked): 20 mg
- Vegetable soup (1 cup): 10 mg
- Fried vegetables (1 cup): 20 mg
- Grilled fish (3 oz): 100 mg
- Poultry (3 oz serving): 50–100 mg
- Legumes (1 cup cooked): 50–100 mg
- Vegetables (1 cup cooked): 5–20 mg
- Fresh fruits (1 medium): 5–10 mg

Activity: No specific activity limitations are necessary for patients with hyperuricemia, but strenuous exercise might raise serum uric acid levels.

Long-Term Monitoring: For patients with symptomatic hyperuricemia, regular follow-up evaluations with serum uric acid level determinations are crucial. For gout patients, maintain uric acid levels between 5–6 mg/dL. Patients with a history of uric acid nephrolithiasis should have 24-hour urine uric acid excretion monitored to ensure therapy efficacy.[8]

Pharmacological Management

Goals of treatment

- Relieve acute symptoms like joint pain, swelling, and inflammation.
- Prevent further uric acid accumulation and crystallization.
- Reduce uric acid levels to prevent kidney damage.
- Prevent chronic gouty arthritis and joint damage.
- Lower cardiovascular disease (CVD) risk associated with hyperuricemia.

- Achieve serum uric acid (SUA) levels <6 mg/dL (or <0.36 mmol/L).

Asymptomatic Hyperuricemia: Treatment for asymptomatic hyperuricemia is debated. The American College of Rheumatology (ACR) does not recommend treatment. The European League Against Rheumatism (EULAR) suggests treatment only if:

- Uric acid levels exceed 10 mg/dL (or >0.60 mmol/L).
- There is a family history of gout or kidney disease.
- Comorbidities such as hypertension or diabetes are present.

Uric acid–lowering drugs should not generally be initiated in asymptomatic hyperuricemia. Focus on addressing modifiable risk factors.

Acute Attack: Treatment of acute gout attacks involves reducing inflammation rather than lowering serum uric acid. If on long-term urate-lowering therapies (e.g., allopurinol, febuxostat), continue their use. Acute attacks can be managed with:

1. ***NSAIDs:*** Full doses (e.g., naproxen 500 mg twice daily) are effective and continued until symptoms resolve (7–10 days).
2. ***Colchicine:*** Effective if administered within 36 hours of an attack. A loading dose of 1.2 mg followed by 0.6 mg 1 hour later is recommended.
3. ***Corticosteroids:*** Useful for those contraindicated for NSAIDs. Administered orally, intravenously, or intra-articularly depending on the situation.
4. ***Interleukin-1 inhibitors:*** Anakinra or canakinumab may be used for hospitalized patients unable to tolerate other treatments.

Management Between Attacks

- Avoid hyperuricemic medications like thiazide and loop diuretics.
- Low-dose aspirin and niacin may increase uric acid levels and should be replaced if alternatives are available.
- Colchicine can be used prophylactically at doses of 0.6 mg once or twice daily to prevent gout flares when initiating urate-lowering therapy.

Urate-Lowering Therapy: This is indicated for patients with.

- Frequent acute arthritis (two or more episodes per year).
- Tophaceous deposits.
- Chronic kidney disease (CKD) stage 2 or worse.

Target Uric Acid Levels

- <6 mg/dL for most cases.
- <5 mg/dL for patients with tophi or frequent attacks.

Drug Options

1. Xanthine Oxidase Inhibitors

- *Allopurinol:* Initial dose of 100 mg/day, increased gradually. Max dose: 800 mg/day.
- *Febuxostat:* Initial dose of 40 mg/day, increased to a max of 120 mg/day.
- Common side effects include hypersensitivity reactions, requiring cessation if a rash develops.

2. Uricosuric Drugs

- Probenecid and lesinurad enhance uric acid excretion.
- Contraindicated in nephrolithiasis or high urinary uric acid excretion.

3. Pegloticase: Administered intravenously for refractory chronic tophaceous gout. Requires rigorous monitoring for hypersensitivity.

Management of Chronic Tophaceous Gout

Effective adherence to allopurinol, febuxostat, or pegloticase can dissolve tophi over time. Serum uric acid levels must be maintained below 6 mg/dL.[9]

Post-Transplant Gout Management

Transplant patients often develop hyperuricemia due to reduced kidney function and medication use. Acute monoarticular gout is best treated with intra-articular corticosteroids. For polyarticular gout, systemic corticosteroids are preferred over NSAIDs or colchicine in cases of compromised kidney function. Long-term management involves urate-lowering therapy with allopurinol or febuxostat.

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