Gout in the elderly

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Abstract

Introduction
Gout is the result of deposition of monosodium urate crystals in and around the joints and soft tissues, due to low solubility of uric acid in hyperuricemic states. It is associated with significant morbidity and mortality from both intra and extra articular complications. There is an increased incidence of gout in the elderly, with the clinical picture differing somewhat from middle age. Additionally, complications may be more severe. The management of gout may be more challenging in the elderly, due to medical co-morbidities, deteriorating metabolic function and drug interactions due to polypharmacy. This review discusses gout and its management in general, with a focus on the presentation and management issues that arise in the elderly.

Conclusion
Gout is a painful condition, which is common in the elderly. Clinical presentation in the elderly can differ from that in the younger people, making diagnosis more difficult. Imaging may be helpful in making a firm diagnosis.

Introduction
Gout is due to deposition of monosodium urate (MSU) crystals in and around the joints and soft tissues. It is common in the elderly with the prevalence rising from 21/1000 in 1990 to 41/1000 in 1999. While gout is commonly considered to be a disease affecting men, this gender difference diminishes after the age of 65, likely due to hormonal influences. Several factors contribute to the high prevalence of gout in the elderly. The risk of gout is related to the duration of hyperuricemia, and hence related to longevity. Increase in cardiovascular, renal, and metabolic morbidity in the elderly, resulting in decreased GFR and reduced uric acid excretion, along with polypharmacy, may precipitate hyperuricemia. The aim of this review is to discuss gout in the elderly.

Etiopathogenesis
Hyperuricemia is defined as serum uric acid (SUA) level over 7.0 mg/dl (450 μmol/L) in men, and over 6.0 mg/dl (360 μmol/L) in women. Hyperuricemia is a prerequisite for the development of gout, but only 10% of people with hyperuricemia will develop gout. Treatment of hyperuricemia with urate lowering therapy (ULT) has been demonstrated to reduce the frequency of acute attacks. This supports a causal association between hyperuricemia and gout.

Uric acid is the end product of dietary and endogenous purine metabolism. In non-primate animals, the uricase enzyme converts uric acid into allantoin, which is highly soluble. Because primates lack uricase, UA accumulates and crystallizes above the physiological saturation threshold (approximately 380 μmol/L or 6.4 mg/dL). The crystalline uric acid (MSU) elicits an intense inflammatory response by release of interleukin-1β (IL-1β) from monocytes and macrophages, causing severe painful inflammatory arthritis.

Uric acid is predominantly produced in the liver (but also in the small intestines); its production depends on purine ingestion, de novo synthesis, and its degradation. As excretion is predominantly through the kidney, with 90% of filtered urate reabsorbed through urate transporter (URAT1) in the proximal convoluted tubules, hyperuricemia is largely a result of renal under excretion.

Serum uric acid levels are affected by many factors, and rising or falling levels can trigger acute gout. Dietary triggers and other risk factors for gout are listed in Table 1. Precipitants in older patients often include drugs, such as diuretics and low dose aspirin. Ethanol abuse, particularly in men, remains a risk factor in the elderly.

Clinical Course
In older people, the clinical presentation is frequently polyarticular, involving the upper limbs. Acute attacks are less frequent in the younger population, with an indolent chronic course and tophii predominating.

Untreated chronic gout is associated with significant morbidity. The most common musculoskeletal complications are acute pain, but joint destruction may result in functional impairment. The most significant extra articular manifestations are renal and cardiovascular. Renal complications include the risk of renal stones and gouty nephropathy, and untreated disease may result in renal failure. This is more likely in older people with longer disease duration and reduced renal reserve. Gout, as part of the metabolic syndrome, confers a significant increased cardiovascular risk, which is the main cause

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Absolute serum uric acid level appears to be an important marker of risk. Higher levels are associated with more frequent acute flares; reducing uric acid level is an important goal.

There are four stages reported in the progression of gout:

1. Asymptomatic hyperuricemia: defined as a persistent SUA of > 6.8 mg/dl without clinical symptoms
2. Acute intermittent gout: characterized by deposition of MSU crystals in the joints and soft tissues, with an intermittent acute and intensely inflammatory arthritis. Typically, acute attacks occur at night, increasing in severity over 24 hours; resolving over 7–10 days. This can present as a systemic inflammatory process associated with fevers, delirium, and biochemical evidence of inflammation.
3. Inter critical gout: describes the asymptomatic periods between acute intermittent gout.
4. Chronic tophaceous gout: characterized by chronic hyperuricemia, leading to increased frequency of acute attacks, progressive shortening of inter critical phase and development of tophi (Figure 1).

### Diagnosis

Clinically, the diagnosis of gout is based on clinical and laboratory findings. The gold standard remains the demonstration of MSU crystals (negatively birefringent needle-shaped crystals) from synovial fluid, tissue or tophi on polarizing microscopy. However, as it is not always possible to get an analysable sample for crystal identification, the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) recognize clinical features that strongly support the diagnosis of gout. These include rapid development of severe

### Table 1: Factors influencing acute gout

<table>
<thead>
<tr>
<th>Factors contributing to increase in risk of acute gout attacks</th>
<th>Factors protective against acute gout attacks</th>
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<tbody>
<tr>
<td>Dietary: High intake of meat, alcohol (beer/spirits) and seafood, sweetened soft drinks, fruit juice or fructose rich fruits (apples and oranges)</td>
<td>Increased intake of dairy products, oat meal and purine-rich vegetable, long-term coffee consumption</td>
</tr>
<tr>
<td>Other: Dehydration, recent surgery, trauma, hospitalization, concentration of serum uric acid level, alcohol consumption, abdominal obesity and physical inactivity, certain medications like diuretics, aspirin, cyclosporine, and initiation of ULT</td>
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</table>

ULT, urate lowering therapy

![Figure 1: Chronic tophaceous gout involving fingers and toes](image-url)
pain, swelling, and tenderness, which reach maximum intensity in 6 to 12 hours; recurrent podagra with hyperuricemia; and more than one attack of acute arthritis. While an elevated SUA is pathogenic in gout, it may be paradoxically normal in acute gout. MRI can also reliably assess early erosions and tophi. It is especially useful in identifying tophi in unusual locations like in the spine.

**Discussion**

The authors have referenced some of their own studies in this review. These studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

**Management**

Management of hyperuricemia and gout should be holistic, encompassing both non-drug and pharmacotherapy. Currently, there are no studies confirming the risk-benefit of pharmacotherapy for asymptomatic hyperuricemia. Until good
Anti-inflammatory pharmacotherapy of acute attacks

The agents commonly used in the management of acute gout are listed in Table 2. Pharmacotherapy of gout in the elderly has unique challenges, outlined in Table 3. In particular, older patients are at risk of adverse effects of medications due to the physiologic changes associated with aging and co-morbidities. Commonly used pharmacotherapy may need to be modified in this setting. Dose adjustment may be required to reduce side effects and to compensate for altered pharmacokinetics, metabolism, and excretion associated with aging. Polypharmacy may increase the risk of drug interactions and toxicity. Pharmacovigilence and monitoring is crucial in the older age group. Treatment modifications often required in the elderly are summarized in Table 3.

Medications used in the treatment of acute attacks include non-steroidal anti-inflammatory drugs (NSAIDs), colchicines, and steroids. ACR 2012 and EULAR guidelines for the management of acute gouty attacks recommend starting pharmacotherapy within 24 hours of the onset of symptoms. Monotherapy or combination therapy can be used depending on the severity of symptoms. Earlier initiation of treatment, after the onset of an acute attack, correlates with a better response rate.

Non-steroidal anti-inflammatory drugs are the drugs of first choice. They are effective and generally well tolerated, if used short-term. However, there is no data to suggest the advantage of any one NSAID in terms of safety or efficacy. In older population, these agents are often not recommended due to toxicity concerns including renal impairment, cardiac failure, or peptic ulcer disease. Co-administration of a proton pump inhibitor may lessen the GI toxicity in some patients.

Colchicine is available in both oral and intravenous formulations. Oral formulations are preferred due to higher toxicity profile of the intravenous formulation. The EULAR guidelines recommend initiation within 72 hours for maximal efficiency. Colchicine toxicity is increased in patients with renal, hepatic, and cardiac impairment, and should be used with caution and appropriate dose adjustments. Less common but severe side effects include neuromyopathy and rhabdomyolysis, which can be fatal, if untreated.

Corticosteroids (CS) are available in oral, intramuscular (IM), and intra-articular preparations (IA). Intra-articular CS may be a safe and effective option in acute mono/oligoarticular gout. Short courses of oral or IM CS evidence exists, pharmacological intervention is not routinely recommended in low risk groups. However, non-pharmacological and lifestyle advice and management of associated conditions are warranted, especially in those with metabolic syndrome or at higher risk. In patients with severe acute, recurrent attacks, or chronic gout, therapy is recommended, unless there are significant toxicity concerns with pharmacological therapy. The goal of management of gout is to rapidly terminate acute attacks and achieve long-term control of hyperuricemia, thereby reducing the sequelae of chronic hyperuricemia.

### Table 2 Drugs used in the treatment of acute gout

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose</th>
<th>Common side effects</th>
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<tbody>
<tr>
<td><strong>NSAIDs</strong></td>
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<tr>
<td>Naproxen</td>
<td>250 mg twice a day, orally</td>
<td>Nausea, vomiting, dyspepsia, gastrointestinal (GI) bleeding, headache, diarrhoea, fluid retention, raised blood pressure, potassium, and creatinine</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>25–50 mg twice or three times a day, orally</td>
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<tr>
<td><strong>Colchicine</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>0.5 mg two to three times daily, orally</td>
<td>Diarrhoea, nausea, and vomiting, which can cause severe dehydration in older people</td>
</tr>
<tr>
<td><strong>Corticosteroids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral prednisolone</td>
<td>0.5 mg/kg/day for 2–5 days followed by gradual tapering and cessation over 10 days</td>
<td>Hyperglycemia, hypertension, infections, mood swings, especially in patients with psychiatric disorders</td>
</tr>
<tr>
<td>Intra-articular steroid*</td>
<td>Dose varies with the joint involved and preparation</td>
<td>Flushing, mild bruising, or bleeding</td>
</tr>
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</table>

*N Septic arthritis must be excluded prior to intra-articular steroid injection.*

**Non-drug therapy**

Patient education is very important in the management of gout. Patients should be informed about the disease, dietary and other triggers of acute attacks, and the importance of compliance with long-term ULT. Specific advice regarding maintaining optimal body mass index (BMI); minimizing alcohol consumption; and restricting offending foods such as crustacean sea foods, high caloric and high fructose beverages and avoiding high purine foods like offal, should be provided to patients. The use of low fat dairy products, fruits, and vegetables should be encouraged.

Table 3  Management of gout in the elderly

<table>
<thead>
<tr>
<th>Therapeutic Guidelines</th>
<th>Therapeutic challenges</th>
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<tbody>
<tr>
<td>1. Patient education, appropriate life style, and dietary advice to reduce the number of acute flare up of gout</td>
<td>1. Atypical presentations can cause diagnostic difficulties and therefore delay the commencement of appropriate management</td>
</tr>
<tr>
<td>2. Urate lowering therapy for asymptomatic hyperuricemia is not indicated</td>
<td>2. Medications that can be used in the treatment can be limited due to associated medical co-morbidities</td>
</tr>
<tr>
<td>3. Avoidance or reduced dose of colchicine in renal, hepatic impairment, and in patients who are also on statins, diuretics, or cyclosporine</td>
<td>3. Consideration should be given to drug interactions due to polypharmacy in the elderly</td>
</tr>
<tr>
<td>4. Avoid NSAIDs in chronic kidney disease</td>
<td>4. Socio-economic and cognitive factors can interfere with medication compliance</td>
</tr>
<tr>
<td>5. Gradual weaning of oral steroids to prevent rebound flare up</td>
<td>5. The number of visits to doctors and laboratory monitoring may be lessened due to poor mobility</td>
</tr>
<tr>
<td>6. Intra articular steroids are preferred options in oligoarticular involvement</td>
<td>6. Most of the trials for newer medications exclude people with multiple medical co-morbidities</td>
</tr>
<tr>
<td>7. Allopurinol is the preferred urate lowering agent. Low starting dose and gradual escalation to achieve minimum target uric acid level of &lt; 0.36 mmol/L. During an acute gout attack, allopurinol should not be stopped if already on it and recent evidence recommends starting allopurinol during an acute attack along with anti-inflammatory or colchicine prophylaxis. Laboratory monitoring for SUA, FBP, creatinine, and LFT is recommended</td>
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<tr>
<td>8. Febuxostat is an option, if allopurinol cannot be tolerated or in cases of allopurinol hypersensitivity syndrome</td>
<td></td>
</tr>
<tr>
<td>9. Colchicine prophylaxis is recommended in the initial 6 months of ULT to prevent acute gout</td>
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<tr>
<td>10. Associated medical co-morbidities should be addressed and adequately managed</td>
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</table>

**NSAIDs, non-steroidal anti-inflammatory drugs; ULT, urate lowering therapy; SUA, serum uric acid; FBP, full blood picture; LFT, liver function test**

may be useful in severe polyarticular involvement, and when colchicine and NSAIDs are contraindicated22, 24.

Other newer options, with limited evidence, for inadequate responders to the above therapy may include IL1 inhibitors like anakinra, canakinumab, and rilonacept. Review of case reports and small randomized controlled trials of these agents suggests that these agents are effective to treat acute gout24. But these are not FDA-approved for use in acute gout24.

**Pharmacotherapy of hyperuricemia in gout**

The ACR guidelines recommend that the diagnosis of gout is established prior to the commencement of ULT.

Indications include the presence of tophi, frequent acute attacks (≥ 2/year), chronic kidney disease (CKD), past history of urolithiasis, and radiographic changes of gout22, 23. The goal of ULT should be a serum urate level of < 360 μmol/L (< 6 mg/dl), or 300 μmol/l (< 5 mg/l) in the setting of tophi21. A decrease in acute flares and a reduction in the size of the tophi have been noted by maintaining target urate level for at least 12 months27. The traditional approach has been to withhold ULT until the acute attack resolves; however, international guidelines recommend that ULT may be instituted during an acute attack, as long as anti-inflammatory therapy has been commenced23.

The EULAR recommends colchicine prophylaxis (0.5–1 mg/day) in the initial six months of ULT to prevent gout flares22. ULT should not be interrupted during any recurrent acute attack.

Current ULT can be divided into those that decrease uric acid production (uricostatic), increase uric acid excretion (uricosuric), or convert uric acid to a soluble product (uricases)22.

**Uricostatic agents**

Allopurinol is the most commonly prescribed ULT in gout, and is considered first line therapy. It is a xanthine oxidase inhibitor. Allopurinol is metabolized in the liver to
oxypurinol, which has a longer half-life and is excreted through the kidney; hence, oxypurinol accumulates in renal impairment. The target uric acid level is often not achieved, especially in the elderly. This is likely to be a result of sub therapeutic allopurinol doses or intolerance. Common adverse events are nausea, vomiting, and diarrhoea. Very rarely, development of allopurinol hypersensitivity syndrome (AHS) has been reported, often in those with renal failure. This is characterized by rash, fever, eosinophilia, vasculitis, toxic epidermal necrolysis, hepatitis, and progressive renal failure. A low starting dose (100 mg/day in any patient and 50 mg/day in patients with CKD stage 4 or worse) decreases the chance of gout flares and the risk of AHS. Gradual dose escalation every 2 to 5 weeks to achieve target serum urate is recommended. Testing for HLA-B*5801 should be considered in select subgroups (Korean descent with stage 3 or worse CKD or of Han Chinese or Thai extraction, irrespective of renal function) with very high risk of developing AHS. Drug interactions, which increase toxicity (including mercaptopurine, azathioprine, cyclosporine, and theophyllines) are common, and should be co-administered with care, or have dose appropriately adjusted and monitored. Febuxostat is approved for use as ULT in gout in people with intolerance to allopurinol or in those who develop AHS. It is a highly selective inhibitor of xanthine oxidase. It is metabolized in the liver and excreted in stool (45%) and urine (49%). Therefore, dose adjustment is not required in mild to moderate renal and hepatic impairment. The drug has not been studied in patients with creatinine clearance < 30 mL/min. Starting dose is 40 mg/day, which could be increased to 80 or 120 mg/day to achieve target serum urate level. Efficacy and tolerability of febuxostat is well-established. Febuxostat 40–80 mg has significantly better urate lowering efficacy than allopurinol 200–300 mg in elderly (≥65 years) population. Side effect profile is similar to allopurinol. Risk of gout flares is similar to that with allopurinol. Patients should also be informed about the risk of flares with the initiation of ULT.

Uricosuric agents
Uricosuric agents (benzbromarone, probenecid, losartan, and sulfinpyrazone) work by inhibiting URAT1. Probenecid is the commonly used uricosuric agent. It is contraindicated in people with urolithiasis and renal impairment (creatinine clearance < 50 mL/min). The risk of renal stone formation during therapy is around 9–11%. The risk is reduced through hydrating and increasing urinary output. Starting dose of probenecid is 250 mg, twice a day for a week or two, and gradually increasing to 500 mg, twice a day, and further to 1 gm, two or three times a day, as needed. Dose of sulfinpyrazole is 50 to 100 mg, twice daily for 1 to 2 weeks, increasing to 100 to 200 mg, twice daily and further to 400 mg, twice daily, as needed. Monitoring of renal function and uric acid excretion is important to reduce the risk of urate nephropathy, renal stones, and renal failure.

Newer agents under study
Recombinant forms of uricase (rasburicase and pegloticase) catalyzes the oxidation of uric acid to soluble allantoin, decreasing the SUA. Rasburicase has a short half-life requiring repeated intravenous administration. Common side effects include allergic and anaphylactic reactions. Pegloticase is approved for treatment in chronic gout, not responding to conventional treatment. This is less antigenic and has a longer half-life than rasburicase. Common side effects include acute gout flares, infusion-related reactions, and antibody formation. Because antibody formation is associated with diminishing response to treatment and worsening infusion reactions, it is recommended that the SUA is monitored and infusions only proceed, if elevated. The use of recombinant uricases is limited by their expense.

Conclusion
Gout is a painful condition, which is common in the elderly. Clinical presentation in the elderly can differ from that in the younger people, making diagnosis more difficult. Imaging may be helpful in making a firm diagnosis. Treatment can be challenging due to other medical co-morbidities, polypharmacy, and drug interactions. Patient education is an important aspect of management. Treatment is directed both at acute flares with NSAIDs, colchicine, and CS and at long-term management of hyperuricemia with urate lowering therapy. The aim should be to maintain the serum urate level < 6 mg/dl.

Management of gout in the elderly requires a comprehensive management plan. This includes eliminating offending risk factors and medications, instituting lifestyle changes, and using appropriate medications at doses that are most likely to be tolerated well by the elderly patient. Monitoring for side effects is essential. Newer less toxic therapies are desirable to reduce toxicity and improve efficacy.

References

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