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DISEASE MANAGEMENT

Educate and treat to eliminate gout flares in elderly patients

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Abstract
Gout flares, caused by monosodium urate crystals in joints, are debilitating and linked to poor health outcomes. Gout prevalence increases with age, but effective treatment is available even in those with associated renal, cardiovascular and metabolic comorbidities. Treatment includes immediate pain relief with low-dose colchicine, non-steroidal anti-inflammatory drugs, or oral/parenteral corticosteroids; with parenteral corticosteroids useful in older patients. Lifelong urate-lowering therapy and patient education, are typically recommended to reduce the risk of recurring gout flares.

Treat gout to avoid unnecessary pain and sequelae

Gout is a manageable form of inflammatory arthritis [1, 2], but it is also the most common form affecting 1–6% of people across the world [2, 3]. Its prevalence and the proportion of women affected both increase significantly with age, with 20% of men aged ≥ 70 years (vs 4.7% of working-age people) self-reporting gout in Australian studies [1] and 4% of female US veterans aged ≥ 80 years affected [3].

Gout flares occur when monosodium urate (MSU) crystals accumulate in joints and periarticular tissues [3], especially the feet and ankles, with the classical presentation being gout in the big toe (podagra) [3]. Gout causes severe pain, reduced mobility, poor sleep, depression, anxiety, and consequent reductions in quality of life [1, 3]. Chronic gout with recurrent flares can damage joints and is linked to poor renal, gastrointestinal (GI), cardiovascular (CV) and infection-related outcomes; all resulting in a 17% increase in overall mortality [4]. The mechanisms of these associations are unclear, including any potential effects from gout treatment [3]. The financial costs of gout in elderly patients are also high [3].

In most patients, gout flares can be completely eliminated and long-term outcomes improved by standard treatment [1, 2]. Despite the availability of guidelines from the American College of Rheumatology (ACR) [5], the European League Against Rheumatism (EULAR) [2] and others, good treatment is usually not provided [1], leaving most patients to experience flares at ever-increasing intervals [6]. This article outlines the recommended management of gout flares in elderly patients, as reviewed by Kumar et al. [3], and relevant recommendations from ACR [5] and EULAR [2] treatment guidelines.

Ask about, don't assume, gout risk factors

Risk factors for gout include hyperuricaemia [elevated serum urate (SU)], older age, male gender, post-menopause, metabolic, CV and renal comorbidities, lifestyle factors (Table 1) and iatrogenic causes [1, 3]. Hyperuricaemia is generally regarded as the first stage of gout [2]. Genetic factors can decrease the excretion of urate from the gut and kidneys, which subsequently results in hyperuricaemia [7]. However, the link between genetics and clinical gout is less clear [7].

Diabetes, obesity, coronary artery disease, hypertension, hyperlipidaemia and nephrolithiasis often coexist with gout [3, 8]. Many of these comorbidities reflect lifestyle and most increase in prevalence as people age [1]. While food and drink may catalyse flares and provide up to one-third of a patient's urate load [3], stigmatising patients is unhelpful [1, 5].

Surgery (including bariatric surgery), severe illness, minor trauma and the early stages of urate-lowering therapy (ULT) can all precipitate flares [3]. Long-term use of diuretics [5], aspirin, cyclosporin and tacrolimus [9], which are all commonly used in older people, increase SU [5]. Age-related

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Table 1 Key lifestyle factors linked to gout flares, as reviewed by Fitzgerald et al. [5] and Richette et al. [2]

Factor	Effect on SU levels	Effect on gout flares
Alcohol		
Consumption in previous 24 h, especially beer	1 unit of beer marginally ↑ SU by 0.16 mg/dL	> 1–2 standard drinks within 24 h associated with 40% ↑ in risk of flare vs alcohol-free periods
Long-term abstention or ↓ intake	1.6 mg/dL (95 µmol/L) ↓ vs no limit	↑ flares in ULT recipients consuming ≥ 30 drinks/wk
Diet		
High-fructose foods, especially corn syrup, but also fruit juice	1–2 mg/dL ↑ (59–119 µmol/L) within 2 h of ingesting 1 g fructose per kg of bodyweight	↑ risk for new flares
Dietary purine, especially from meat and seafood	No change in 29 pts well educated about diet, receiving ULT	↑ risk of attack with excessive meat intake; dose-response relationship between purine intake and flares
Low-fat dairy food, cherries, coffee	Milk is uricosuric, ↑ renal uric acid secretion and ↓ SU	Cherry consumption may ↓ gout flares; coffee and cherries linked to ↓ gout incidence
Weight		
Obesity and changes in BMI	2 mg/dL (119 µmol/L) ↓ in 12 pts who received bariatric surgery and lost a mean of 34 kg bodyweight in 1 yr	↑ in new-onset gout (but not recurrent flares) with obesity; 5% ↑ in BMI linked to 60% ↑ in recurrent flare and 5% ↓ in BMI associated with 40% ↓ in recurrent flare

BMI body-mass index, *pts* patients, *SU* serum urate, *ULT* urate-lowering therapy, ↑ increase(d), ↓ decrease(d)

decline in renal and hepatic function may decrease renal urate clearance and exacerbate these effects [1].

Treatment for asymptomatic hyperuricaemia is not recommended

The relationship between asymptomatic hyperuricaemia (AH) and gout flares is unpredictable [3]. AH is common and linked to increased mortality [2], but even very high SU levels may never cause a gout flare [3]. In one 5-year study, only 20% of people with SU > 9 mg/dL developed gout [5]. Despite poor non-gout outcomes, for cost-benefit reasons, the pharmacological management of AH (defined as SU > 6.8 mg/dL or 400 mmol/L) is not recommended, including in patients with chronic kidney disease (CKD) or other comorbidities [5].

Both gout and hyperuricaemia are also strongly linked to CKD [2], with 86% of people with SU >10 mg/dL (595 µmol/L) having stage 2 or worse disease; 53% of gout patients in the same study had CKD [2]

Flare, crystals and serum urate all add up to gout

Patients with gout may have a history of risk factors, previous flares and/or elevated SU [3]. Those with a classic flare report a sudden onset of pain in one peripheral joint or bursa, which may appear warm, swollen and red. Use of the joint, pressure or even touch may be unbearable. Tophi, which are subcutaneous nodules, may be present in joints and suggest advanced disease. Patients may also present with fever and leucocytosis; aseptic cellulitis and other forms of arthritis, including septic arthritis, must be excluded [3].

Chronic, advanced disease also increases in frequency with age [10]. In approximately half of patients aged > 65 years, subacute flares in several joints occur concurrently [10]. Taking a careful history and utilizing gout scoring systems can help confirm a diagnosis where presentation is atypical [2, 3, 5].

In patients with probable gout, diagnosis may be confirmed in 95% of patients by measuring SU and assessing the synovial fluid or tophus aspirate for needle-shaped MSU crystals whilst excluding infection [11]. Repeating the analysis for SU some weeks later is suggested, as levels can drop during a gout flare, often to normal [12].

Imaging may be appropriate [3], particularly where the diagnosis is unclear [5]. Dual-energy CT is sensitive and specific for gout, particularly for the atypical presentations common in older patients [3], and ultrasound is recommended by the ACR and EULAR [2, 5]. Imaging facilitates fluid aspiration procedures, and may also reveal tophi or the double-contour sign; this sign is highly specific for gout as it shows the deposition of MSU crystals across hyaline cartridge [12].

In older patients, kidney and hepatic function tests, including an estimate of creatinine clearance (CL_{CR}), plus other investigations relevant to known or suspected comorbidities (e.g. glycosylated haemoglobin for diabetes) are recommended [3]. EULAR guidelines recommend screening

for CKD, heart failure (HF), hypertension and peripheral artery disease, smoking, diabetes and lifestyle [2]. Such screening systematically elucidates polypharmacy, and resultant potential drug interactions, that are common in older patients (Table 2) [1].

Approach flare treatment from all angles

The aspects of gout flare treatment should be discussed with patients [3]. The immediate need is the relief of acute pain and inflammation (Table 2); however, over the longer-term, lifelong ULT, along with lifestyle changes, are usually recommended to prevent further flares [2, 5]. Prophylaxis against repeat flares early in ULT is also recommended as they are paradoxically more likely as MSU crystals disperse from joints [2].

Reviewing non-gout medications is also recommended [2, 5]. When gout flares occur in hypertensive patients receiving thiazide or loop diuretics [2], these should be replaced where possible with losartan (an angiotensin-converting enzyme inhibitor) or calcium channel blockers [2]. Patients with hyperlipidaemia may benefit from a statin (subject to colchicine interactions, Table 2) or fenofibrate [2], although the latter is not a recommended switch in the USA [5]. Low-dose aspirin, where clearly indicated, should be continued in the absence of alternatives [5].

Choose from three helpful first-line flare choices

While gout flare management in older and/or renally impaired patients may be more complex than in younger people, treatment options that may preserve kidney and CV function are available (Table 2) [2, 3, 5]. Selecting an appropriate first-line acute flare therapy in an older patient depends on their profile (Table 2), including comorbidities and the potential for adverse drug events (ADEs) [3]. Recommendations in severe CKD vary, especially with colchicine (Table 2) [2, 13].

Using colchicine only at low doses ($\leq$ 1.2 mg and $\leq$ 0.6 mg 1 h later) is consistently suggested (Table 2) [2, 5] as it results in GI ADEs similar to placebo (e.g. nausea and diarrhoea), with no drop in efficacy versus a higher dose (4.8 mg over 6 h) [14]. A 24 h drug-free interval on day 2 (Table 2) may also reduce colchicine ADEs [1]. In older people, where colchicine is contraindicated, selecting shorter-acting non-steroidal anti-inflammatory drugs (NSAIDs) may likewise minimise ADEs (Table 2) [1].

Parenteral corticosteroids may be preferred for patients who have comorbidities that are contraindications to colchicine or NSAIDs and/or have significant drug interactions, as is often the case in older patients (Table 2). If oral corticosteroids are used, systemic ADEs should be discussed with patients (Table 2) [5].

Conversely, for severe flares such as tophaceous gout or if multiple joints are affected [2], combination therapy such as colchicine in combination with NSAIDs or glucocorticoids may be tolerated, although high quality efficacy data are lacking [3]. Concomitant NSAID and glucocorticoid use is not recommended due to potential GI toxicity [3].

Adjuvant therapies such as topical ice [5] and limited use of non-NSAID analgesics may be helpful [3]. Opioids are widely dispensed to gout patients, despite their routine use not being recommended in guidelines [2, 5]. Opioids are especially inappropriate in elderly patients with CKD and other comorbidities in whom ADEs are likely [3].

Interleukin-1 antagonists are second-line options

Limited data support the use of subcutaneous injections with interleukin (IL)-1 blockers, anakinra and canakinumab, as second-line options for recurrent flares [2, 5]. IL-1β influences MSU-induced inflammation and IL-1 blockers may have a future role in gout prophylaxis [2]. Anakinra 100 mg/day for 3–4 days [16] and canakinumab 150 mg as a single dose were each at least as effective as intramuscular (IM) triamcinolone [2]; the shorter half-life of anakinra may be helpful in older patients [3]. Occult sepsis must be excluded before IL-1 inhibitors are started, and ULT adjusted after their administration [2]. Despite their efficacy, access to IL-1 inhibitors may be limited due to cost in the USA [5].

While IM adrenocorticotropic hormone 1 mg acts quickly with similar efficacy to triamcinolone [6], it is a third-line option in the US and not recommended in Europe [2, 5] due to cost, inaccessibility and limited tolerability data [3].

Long-term treatment and patient education are important

All patients with recurrent flares should receive lifelong ULT [2, 5]. Preventing repeat flares with ULT is a key therapy goal [2, 5] and they may be eliminated if patients adhere to treatment [2]. ULT aims to reduce SU to concentrations below where it crystallises (< 6 mg/dL or 360 µmol/L) [8], as a treat-to-target approach [2, 5]; the risk of gout increases above this target [2, 5, 9]. In severe gout, the target is 5 mg/dL (300 µmol/L) to speed MSU crystal dissolution [2]. The benefits of lowering SU to < 3 mg/dL are not clear and this is not currently recommended [2].

At present, many patients are not given the option of ULT, and in patients who are offered long-term ULT, approximately half discontinue treatment [1]. Adherence significantly improves with patient education, with 92% of better

Table 2 First-line pharmacological treatments for older patients with acute gout flares, as reviewed by Kumar et al. [3]

Therapeutic agent	Comments
Colchicine (oral)	
Place in therapy	First-line option for flares, initiate within 12 h of onset; first-line prophylaxis against repeated flares [2, 13]
Dosage for acute flares	1–1.2 mg at onset, then 0.5–0.6 mg 1 h later on day 1, in line with available formulations [1, 3, 5], 0.5–0.6 mg once or twice daily from day 2 [3] or 3 [1] until flare resolves, usually in 5–10 days
Dosage for flare prophylaxis	0.5–0.6 mg/day for 6 months in pts starting ULT [2]
Elderly pts	Base dosage on renal function [13]
Severe CKD[a]	European consensus: avoid, contraindicated in some countries [2]; US PI: normal dose for flares for ≤ 14 days and ↓ starting dose to 0.3 mg/day for prophylaxis [13]
	Monitor closely if ↑ prophylaxis dose and consider alternatives in pts with repeated flares [13]
	In pts requiring dialysis: ↓ dose to 0.6 mg 2 weekly for flare, start at 0.3 mg 2 × weekly for prophylaxis [13]
Mild–moderate CKD[a]	For long-term prophylaxis, ↓ dose to avoid neurotoxicity or muscular toxicity [2]; however, dosage adjustments are not typically required with a dosage of 0.5–0.6 mg/day [15]
Hepatic impairment	No dose adjustment needed with mild–moderate impairment; limit treatment duration for flares to 14 days and consider a ↓ dose for prophylaxis [13]
CVD	First-line option, safe and may be beneficial in coronary heart disease [2, 8]
Contraindications	Pts with renal or hepatic impairment receiving P-gp or strong CYP 3A4 inhibitors [13]
Drug interactions	Avoid with strong CYP 3A4 and 3A5 [1] inhibitors and/or P-gp inhibitors (e.g. clarithromycin, cyclosporin, diltiazem, ketoconazole, ritonavir, verapamil) [1, 2] and ↓ dose by 50% with other moderate-strong CYP 3A4 inhibitors, e.g. protease inhibitors, erythromycin [13]
	Statin coadministration may cause neurotoxicity or muscular toxicity including rhabdomyolysis [2]
	Avoid concurrent non-steroidal anti-inflammatory agents in elderly gout patients [3]
Non-steroidal anti-inflammatory agents (oral)	
Place in therapy	First-line option for flares, initiate at symptom onset; second-line for prophylaxis where colchicine is not tolerated [2]
Dosage for acute flares	5–10 days as per PI, e.g. naproxen 500 mg bid for 5 days is equivalent to 35 mg/day of prednisolone for 5 days [2]
Dosage for flare prophylaxis	Low dose, e.g. naproxen 250 mg twice daily for ≤ 6 months ± proton pump inhibitor [2]
Elderly pts	Short-term use of options with a short half-life is preferred e.g. naproxen, ibuprofen [3]; in pts with ↑ risk of GI bleeding or perforation, coadminister proton pump inhibitor [1]
CKD[a]	Avoid in pts with severe CKD; minimise use in pts with moderate CKD [2, 3]
CVD	Last-line option for acute flares in pts with CVD and avoid in HF [8]
Contraindications	Severe CKD or HF, concurrent anticoagulants, peptic ulcer disease, ischaemic heart disease [1, 8]
Drug interactions	In elderly pts, ↑ likelihood of interactions due to polypharmacy, particularly diuretics; avoid concurrent colchicine use in elderly pts [3]
Corticosteroids (oral, intra-articular, intramuscular or intravenous [5]**)**	
Place in therapy	First-line option for flares, especially in older pts and/if oral administration is not possible [1, 5]
Dosage for acute flares (oral)	Prednisolone 30–35 mg/day or equivalent for 5 days [2]; or ≥ 0.5 mg/kg/day for 5–10 days; or full dose for 2–5 days tapered to zero over 7–10 days [6]
Elderly pts	↓ dosage e.g. prednisolone 25 mg/day for 2 days, then taper over 3–4 days [1]; if practicable, use intra-articular administration for flares in single joints, to ↓ systemic ADEs [2, 3]
	Monitor for common ADEs, including cognitive impairment, electrolyte abnormalities, hypertension, hyperglycaemia, infections, sleep disturbance [3]
CVD	Second-line option, short-term use may not affect HF but long-term use associated with poor CVD outcomes [8]
Contraindications (for systemic agents)	Active infection, impaired wound-healing, poorly controlled diabetes [3]

ADEs adverse drug events, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *CYP* cytochrome P450, *GI* gastrointestinal, *HF* heart failure, *P-gp* P-glycoprotein, *PI* prescribing information, *pts* patients, *ULT* urate-lowering-therapy, ↓ decrease(d) ↑ increase(d/ing)

[a]Severe CKD is defined as creatinine clearance < 30 mL/min, mild–moderate CKD as creatinine clearance ≥ 30 mL/min

informed patients effectively treated after 1 year in an observational study [2]. Furthermore, patients should be included in the decision making process to improve adherence [2].

Potential ADEs and the possibility of flares early in the course of ULT should be discussed, so that patients understand that either medications or dosages can be changed if needed, rather than discontinuing ULT [2]. Early flares caused by the dissolution of MSU crystals can be minimised by a gradual start to ULT and the use of prophylactic treatments (Table 2), with colchicine preferred in most older patients [1]. Patients may alternatively be prescribed on-demand medication to take as soon as flare symptoms occur [3]; the immediacy of on-demand treatment should be emphasised (Table 2) [2].

Patient education and encouraging lifestyle changes should always be a part of gout management (Table 1) [2]. Certain foods and drinks, such as beer or meat, are recommended to be consumed in moderation [2]. Weight loss and regular exercise are recommended for all patients (Table 1) [2, 5].

Long-term use of low-dose colchicine may also be effective in the prophylaxis of gout flares (Table 2) [15]. Safety concerns relating to cancer or infection risk with long-term colchicine was reported in one trial; however, other trials did not corroborate this result and its safety is supported by 50 years of clinical experience [15]. While many patients decline prophylaxis without experiencing numerous flares, low-dose colchicine may have other benefits. For instance, colchicine reduced major CV events in two trials in patients with coronary heart disease [2].

Eliminate flares with urate-lowering therapy

ULT should be started during or after a first flare [2], where:

- patients have urolithiasis, moderate to severe renal [5] or CV comorbidities, such as HF, hypertension or ischaemic heart disease [2], all of which affect many older patients [1]; and/or
- SU is very high (> 8 or 9 mg/dL or > 480 or 535 µmol/L [2, 3, 5]; and
- patients aged < 40 years (EULAR recommendation) [2].

In the US, starting ULT during a flare is recommended for practical reasons as patients are with their clinicians and motivated to consider therapy [5]. Regular SU testing is an essential part of ULT due to its treat-to-target goals, and nurse- or pharmacist-led programmes are helpful [5].

Use allopurinol, subject to genetic risks

The xanthine oxidase inhibitor (XOI) allopurinol is the first-line option for ULT [2]. Starting ULT with low doses and titrating to target is an effective and well tolerated approach, including in older patients [5]. In patients of Asian and African origin, genetic testing is recommended prior to starting allopurinol due to the higher risk for severe hypersensitivity [1]. There are also several provisos relevant to older patients with CKD:

- In mild-moderate disease ($CL_{CR} \geq 30$ mL/min) allopurinol may be replaced with febuxostat starting at ≤ 40 mg/day [5], or added to/replaced with the uricosurics benzbromarone or probenecid [2], although hepatotoxicity is a problem with the latter [1].
- In moderate-to-severe disease, a dose reduction of ≥ 50% based on CL_{CR} is recommended [2, 5].
- The preferred second-line option in this group is an XOI [1] (e.g. febuxostat starting at ≤ 40 mg/day) despite its CV [1] and mortality [17] risks, rather than probenecid starting at 500 mg once or twice daily [5].
- In severe, chronic, tophaceous gout with poor life quality, pegloticase is a second-line option due to cost and tolerability issues [2, 5].

Take home messages

- Gout flares, caused by MSU crystal accumulation in and around joints, are painful and debilitating; both immediate management of pain and inflammation in addition to long-term preventative strategies are required.
- Colchicine, NSAIDs and oral or parenteral corticosteroids (parenteral corticosteroids are well suited to elderly patients) are all first-line options for treating gout flares.
- The presence of comorbidities (e.g. CKD or CV) and the potential for pharmacokinetic drug interactions may guide treatment selection.
- Comorbidities and polypharmacy in older people, who are most prone to gout, do not preclude the effective treatment and eventual elimination of gout flares.
- Effective patient education and long-term ULT (typically with allopurinol) can prevent the recurrence of gout flares, improving quality of life and long-term renal and CV outcomes.

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