

REVIEW

Gout flare in the critical care setting: diagnostic challenges and treatment options

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Abstract

Gout is the most common form of crystal-induced arthritis. Gout flares are a frequent complication during hospital admissions, including the critical care settings. Inpatient gout flare is a multifactorial event influenced by a combination of gout- and hospitalization-related factors. Several factors can trigger gout flares through altered renal urate handling, serum urate fluctuation, and macrophage priming. Early detection of gout flares can aid in the reduction of unnecessary antibiotics use, laboratory investigations, and diagnostic procedures, leading to improved hospital outcomes. Identification of crystals in synovial fluid or tophi is the gold standard for gout diagnosis, but the procedure is sometimes contraindicated in the critical care setting. Hospitalized patients with gout usually have multiple comorbidities contributing to challenges in the management of gout flares, which are not present in outpatient or noncritical inpatient settings. In this review, we discuss the unique characteristics and impact of gout flares in the critical care setting, as well as the diagnostic challenges and options for the treatment of gout flares and hyperuricemia in this setting.

Keywords

Gout; Hospitalization; Critical care; Uric acid; Urate-lowering therapy; Arthritis

1. Introduction: why should we care about inpatient gout flares?

The prevalence of gout, which is the most common form of crystal-induced arthritis especially in men, ranges between 1% and 4% in the general population from high-income countries [1]. Gout results from prolonged elevation in total body uric acid pool, which subsequently leads to the deposition of monosodium urate (MSU) crystals in joints and surrounding tissues. The deposited MSU crystals can trigger episodes of intense inflammatory response termed gout flares. Patients who develop a gout flare typically experience severe pain and swelling of the affected joint which can prevent joint utilization. Gout is primarily considered as an ambulatory issue, and most gout cases in clinical and epidemiological studies are recruited from primary care or outpatient populations.

Gout flares can be both a cause and complication during hospital admission. Inpatient gout flare is a common clinical presentation in hospital-based practice. A retrospective study from New Zealand reported that gout accounted for 0.12% of all acute admissions and that gout was a complicating diagnosis in 0.15% of all admissions [2]. A study from the USA found that 13% of hospitalizations were in the intensive care setting in a survey of 454 hospitalizations in patients with gout [3]. According to a study from Australia and New Zealand, cardiovascular disease, infection, stroke, and arrhythmia were the most common primary admission diagnoses in hospitalized

patients with gout flare as a complicating diagnosis [4].

The risk of gout flares increases during hospitalization in patients with established gout. Individuals with gout are estimated to be at 10-fold higher risk for gout flares during hospitalization compared to the outpatient setting, and the rate of in-hospital flare increases with the duration of hospital stay [3, 5]. Numerous factors present in the inpatient setting can trigger gout flares through altered renal urate handling, changes in serum urate concentration, and priming of inflammatory cells. Possible triggers of inpatient gout flares include volume depletion, acidosis, surgery, and medications affecting urate concentration [6].

People with critical illness are especially vulnerable to in-hospital complications and poor outcomes among the inpatient population. Inpatient gout flares in these individuals may lead to more invasive investigations such as joint aspiration and treatments such as anti-inflammatory agent use, which subsequently put patients at additional risk for in-hospital complications. Additionally, the detection and diagnosis of gout flares in the critical care setting can be challenging because the signs and biomarkers of inflammation become less reliable in the context of critical illness. Furthermore, comorbidities may further limit the treatment options for gout flares. Despite these unique challenges, studies on this particular population remain limited. This review describes the mechanisms and risk factors of gout flare and summarizes challenges in its diagnosis and treatment in the critical care setting.

2. What are the possible triggers of gout flares in a critical care setting?

Gout flare is an inflammatory response to the MSU crystals in joints and surrounding tissues. Gout flares may develop following any event that leads to the alteration of microenvironment around microtophi in the synovium and articular cartilage. Destabilization of microtophi leads to the shedding of MSU crystals into the joint space that subsequently trigger inflammatory response or gout flares [7]. The NACHT-LRR-PYD-containing protein 3 (NLRP3) inflammasome is present primarily in immune cells such as macrophages after activation by inflammatory stimuli, such as critical illness. Activation of the NLRP3 inflammasome appears to occur in two steps. The first step involves a priming signal in which many pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs) are recognized by toll-like receptors (TLRs), leading to activation of nuclear factor kappa B (NF- κ B)-mediated signaling, then up-regulates transcription of inflammasome-related components. The second step is the oligomerization of NLRP3 and subsequent assembly of NLRP3, adapter protein apoptosis-associated speck-like protein (ASC), and procaspase-1 into a complex, which triggers the transformation of procaspase-1 to caspase-1 and the production of mature interleukin (IL)-1 β and IL-18 [8]. The other inflammatory mediators that are well described in gouty inflammation are IL-8, IL-6, tumor necrosis factor- α , and multiple prostaglandins and leukotrienes (e.g., leukotriene B4) [9]. Eventually, neutrophils and other inflammatory cells are recruited to the affected joint, leading to further inflammation.

Inpatient gout flare is a multifactorial event influenced by a combination of gout-related and hospitalization-related factors. Although no study to date has examined predictors of gout flares exclusively in the critical care setting, several studies have evaluated factors associated with gout flares in the general inpatient setting [10–13].

Factors that may increase the risk of gout flares during hospitalization are volume depletion, over-hydration, worsening renal function, acidosis, surgery, diuretic use, and adjustment of gout medications [6, 14]. These factors may alter serum urate levels to subsequently promote crystal dissolution and shedding in individuals with decreased serum urate; they may otherwise promote crystal formation in individuals with increased serum urate levels.

Multivariate analyses reveal cancer surgery, three-day presurgical urate level >0.54 mmol/L, and absence of colchicine prophylaxis as risk factors for postsurgical gout attacks. Postsurgical gout flares are speculated to be triggered by a transient decrease in serum urate level caused by intravenous infusion of low-sodium fluid during the perioperative period in combination with lower resorption of filtered urate in proximal renal tubules by sodium-dependent organic acid cotransporters [10, 11].

In a retrospective study of 920 patients admitted for stroke in Taiwan, the prevalence of gout flares was 6.5% among patients with stroke. Gout flare during stroke hospitalization was associated with history of gout and serum uric acid level (odds ratio [95% confidence interval], 14.28 [6.75–30.18] and 1.49 [1.26–1.78], respectively). Hypercholesterolemia was

also associated with gout flares (odds ratio [95% confidence interval], 2.01 [1.06–3.83]), which might be explained by the correlation of hyperlipidemia with alcohol intake, obesity, and genetic defects [12]. Jatuworapruk *et al.* [13] identified nine predictors of inpatient gout flares in patients with comorbid gout: preadmission serum urate level >0.36 mmol/L, no use of preadmission urate-lowering therapies (ULT), absence of preadmission gout flare prophylaxis, ULT adjustment, initiation, or increased dose of gout flare prophylaxis, tophus, diuretic adjustment, acute kidney injury, and surgery. These predictors were likely to be associated with gout flares by causing sudden changes in serum urate levels or due to the suboptimal control of gout, all of which increased the risk of gout flares. Table 1 (Ref. [10–13]) summarizes factors associated with in-hospital gout flares.

3. Does my patient have a gout flare?

Typical presentation of gout flares includes acute swelling and tenderness of a single joint (monoarthritis), which often reaches maximum intensity in less than 24 hours. The most commonly involved joints are first metatarsophalangeal (MTP1), tarsal, ankle, and knee joints (Fig. 1) [15]. Oligoarticular or polyarticular involvement may occur especially in patients with long-standing, untreated disease or during hospitalization [15]. Oligo- and polyarticular flares can be associated with systemic manifestations including fever, chills, and elevated levels of inflammatory markers [16]. Physical examination of the affected joint usually reveals one or more of the following findings: skin redness over and around the joint, joint swelling, warmth, tenderness, and limited range of motion. During a gout flare, pain can be so severe that patients may be unable to bear touch or pressure to the affected joints. In patients with advanced gout, subcutaneous nodules (tophi) may be found at distal joints, finger pads, ear pinnae, olecranon bursae, and tendons [17].

Detection of gout flares can be difficult in the critical care setting. Patients may have coexisting infections or systemic inflammatory response syndrome, which can obscure the common clinical features of gout flares, including pain and fever. Patients with impaired consciousness may not be able to communicate the presence of joint pain that can potentially facilitate the detection of gout flares.

Identification of MSU crystals is the gold standard for gout diagnosis. MSU crystals in synovial fluid and tophus aspirates appear as strongly birefringent, needle-shaped crystals with negative elongation under polarized light microscopy (Fig. 2). However, joint aspiration is sometimes contraindicated in the critical care setting due to various reasons, such as bleeding disorders and infection of the overlying skin. Clinical diagnosis is therefore based on suggestive features of gout flares: monoarthritis of a foot or ankle joint; history of gout or episodic arthritis, and presence of tophus and/or hyperuricemia [18].

Serum urate level is not a reliable indicator of gout flares. Normal serum urate levels have been reported during gout flares, which could be explained by the increased urinary excretion of uric acid during the flare [19]. Patients receiving long-term allopurinol treatment were more likely to have lower

TABLE 1. Factors associated with in-hospital gout flares.

Factors	OR (95% CI)	Reference
Presurgical uric acid level >0.54 mmol/L	8.25 (2.23–30.54)	[10]
Cancer surgery	6.19 (1.92–19.90)	[10]
Colchicine prophylaxis	0.16 (0.04–0.61)	[10]
Previous flares involving ankle	5.63 (1.63–19.41)	[11]
Decrease in postsurgical SU level by ≥ 0.126 mmol/L	19.73 (8.13–47.89)	[11]
Abdominal surgery	3.37 (1.18–9.62)	[11]
Gout history	14.28 (6.75–30.18)	[12]
Uric acid level	1.49 (1.26–1.78)	[12]
Hypercholesterolemia	2.01 (1.06–3.83)	[12]
No preadmission ULT	4.40 (2.50–7.87)	[13]
ULT adjustment	3.04 (1.31–7.03)	[13]
Diuretics adjustment	2.91 (1.58–5.39)	[13]
Preadmission SU level >0.36 mmol/L	3.36 (1.31–8.61)	[13]
Tophus	4.32 (1.39–13.40)	[13]
No preadmission gout prophylaxis	8.44 (2.26–31.57)	[13]
Initiation or increased dose of gout prophylaxis	17.36 (2.76–109.24)	[13]
Acute kidney injury	2.33 (1.23–4.43)	[13]
Surgery	1.84 (1.01–3.38)	[13]

CI, confidence interval; OR, odds ratio; SU, serum urate; ULT, uric acid-lowering therapy.



FIGURE 1. Gout flare at the right first metatarsophalangeal (MTP1) joint in a hospitalized patient. Right MTP1 joint appears swollen and erythematous indicating severe inflammation.

serum urate levels during a gout flare, compared with patients who were not taking allopurinol.

High peripheral blood leukocyte count and increased levels of acute-phase reactants such as C-reactive protein are not reliable diagnostic tools for gout flares. These parameters only indicate the presence of inflammation and do not point to its

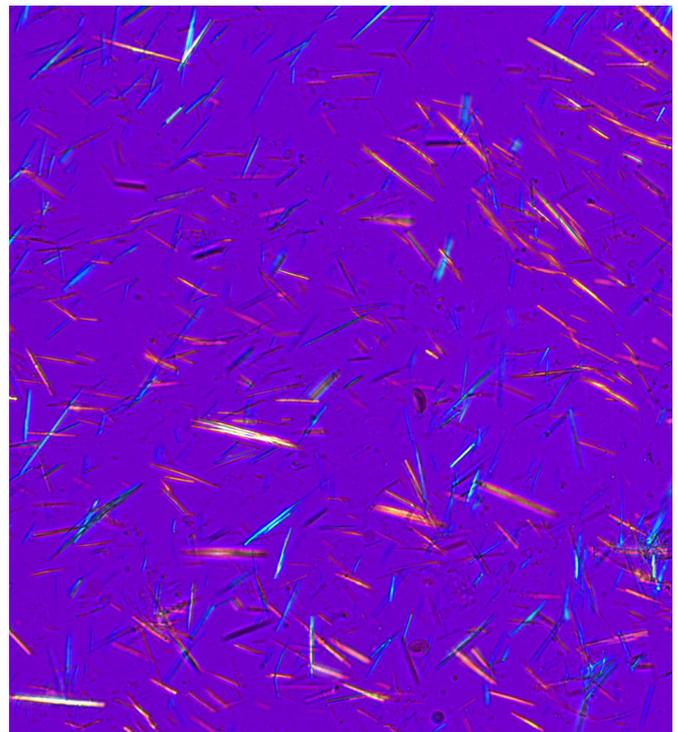


FIGURE 2. Monosodium urate (MSU) crystals examined under polarized light microscopy.

cause [20]. Furthermore, high leukocyte count in the synovial fluid is not helpful in distinguishing gout from other arthritic conditions. Synovial fluid leukocyte count can even be in the septic range ($>50,000$ cells/mm³) during a gout flare.

Plain radiography has limited value for diagnosing gout flares, because the presence of soft tissue swelling or joint effusion in plain radiography is only an indicator of arthritis and does not provide information on the specific etiology.

Gout-specific radiographic findings including punchout bone erosion and overhanging edge appearance may support the diagnosis of gout flares. However, these specific findings are only observed in patients with advanced tophaceous gout [21].

Ultrasonography is of significant interest for gout diagnosis because of low cost, widespread availability, no radiation exposure, and suitability for the critical care setting. Sonographic depositions of MSU crystals on the surface of articular cartilage, detected as the double-contour sign, and presence of tophus are helpful for the diagnosis of gout flares by ultrasonography, especially if accompanied by evidence of inflammation such as soft tissue swelling, joint effusion, and increased blood flow by Doppler ultrasonography. A large, multi-center, cross-sectional study using MSU positivity as the gold standard for gout diagnosis in 824 patients found that the presence of one of these features had a sensitivity and specificity of 76.9% and 84.3%, respectively [22].

Dual-energy computed tomography (DECT) is a non-invasive imaging modality that allows for the accurate and reproducible quantification of MSU deposits using automated software techniques. DECT is also used to identify and diagnose gout; it enables the detection of MSU deposition in anatomic structures that cannot be easily aspirated or where there is insufficient joint fluid. However, DECT appears to have limited sensitivity in patients with acute gout and no prior episodes of gouty arthritis [23, 24].

In addition to gout flares, the differential diagnosis of acute arthritis in the critical care setting should also include septic arthritis, calcium pyrophosphate (CPP) crystal arthritis and periarticular inflammation such as cellulitis and thrombophlebitis. Septic arthritis is often a major concern in patients with concurrent blood stream infection or infection adjacent to the joint. The clinical features of acute gout and septic arthritis are sometimes difficult to distinguish because both conditions typically cause severe arthritis accompanied by the systemic inflammatory response. Synovial fluid leukocyte count may exceed 50,000 cells/mm³ in both conditions, and a creamy pus-like fluid termed urate milk may be found in patients with very high MSU crystal content in the joint [25]. Concurrent gout and septic arthritis have also been reported, and the finding of MSU crystals does not always exclude septic arthritis [26]. Gram staining and culture of the synovial fluid are therefore important to establish the diagnosis of septic arthritis.

CPP crystal arthritis can also mimic gout flares especially in older patients. A cross-sectional study from Thailand has reported that, compared to patients with gout flares, those with CPP arthritis were more likely to develop monoarthritis and had normal serum urate levels during the arthritis episode [27]. Identification of positively birefringent, rhomboid-shaped crystals in synovial fluid is the best evidence to support the diagnosis of CPP crystal arthritis. Other possible differential diagnoses of acute arthritis in the critical care setting include osteoarthritis with acute inflammation in older patients and hemarthrosis in patients with bleeding disorders. Table 2 (Ref. [27, 28]) summarizes major differential diagnoses of acute arthritis and key distinguishing features in the critical care setting.

4. Management of gout flares: balancing between efficacy and safety

Gout treatment has two components: resolution of pain and inflammation caused by gout flares and long-term management to lower serum urate to a target level of <0.36 mmol/L to remove MSU crystal deposits from the body and reduce the frequency of future episodes.

In most guidelines, the recommended first-line therapeutic options for gout flares are oral nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and low-dose colchicine [29–31]. The choice of medication is guided by concomitant clinical conditions that preclude the safe use of a particular regimen as well as by the severity of gout. There are no head-to-head trials comparing the efficacy of these three therapeutic options. However, randomized trials comparing NSAIDs with corticosteroids or colchicine suggest that all three options exhibit comparable efficacy and safety profiles for the treatment of gout flares [32, 33]. However, it must be emphasized that these clinical trials were conducted in outpatient or primary care settings where the patients were not as vulnerable as those in the critical care setting. Combination therapy with NSAIDs plus colchicine or with colchicine plus corticosteroids may be considered in patients with severe polyarticular flare or in cases where monotherapy does not lead to sufficient response within 24 hours [34]. Other anti-inflammatory agents such as IL-1 inhibitors may be considered in exceptional cases with contraindications to all first-line agents.

4.1 NSAIDs

NSAIDs with rapid onset of action are effective in treating gout flares. Typical doses for treating gout flares are 500 mg twice daily, 50 mg three times daily, and 120 mg once daily for naproxen, indomethacin, and etoricoxib, respectively [35, 36]. NSAIDs may not be suitable for many patients in the critical care setting due to comorbidities such as acute kidney injury, heart failure, myocardial infarction, gastrointestinal bleeding, hyperglycemia, active infection, and drug interaction. Therefore, NSAIDs should be used if necessary and discontinued as soon as the flare is resolved.

4.2 Colchicine

Low-dose colchicine (1.2 mg followed by 0.6 mg after one hour) is the preferred regimen. The efficacy of this regime is comparable to that of high-dose colchicine, with a safety profile indistinguishable from that of placebo [37]. After treatment initiation, continued therapy includes 0.5–0.6 mg colchicine once or twice daily, which is started 12 hours later until the resolution of gout symptoms [38]. In patients with chronic kidney disease, dose reduction is not necessary but treatment should not be repeated more than once every two weeks given the increased risk of myotoxicity and neurotoxicity. A single colchicine dose of 0.6 mg is recommended for gout flares in patients with end-stage renal disease [39]. Colchicine is most effective when administered early, typically within 48 hours after flare onset due to its mechanism of

TABLE 2. Major differential diagnosis of acute arthritis in the critical care setting [27, 28].

Disease	Personal history	Onset	Typical pattern of joint involvement	Joints affected	Associated features	Synovial fluid findings
Gout	Male, postmenopausal women	Sudden	Monoarticular	first metatarsophalangeal (MTP1)-most common), tarsal, ankle, knee	Tophi	MSU crystals (strongly birefringent, needle-shaped crystals)
CPPD	Elderly (>60 years)	Sudden	Monoarthritis or oligoarticular	Knee (most common), wrist	Fever, systemic symptoms	Positively birefringent, rhomboid-shaped crystals
Septic arthritis	Elderly (>80 years), immunocompromised, prosthetic joint	Acute	Monoarticular	Knee (most common), hip, shoulder, ankle, wrist	Fever, systemic symptoms	Inflammatory range (WBC count >50,000 cells/mm ³) Gram stain positive in 50%, culture positive in 90%
Hemarthrosis	Young male	Acute	Monoarthritis	Knee, elbow	Hemophilia- prodromal stiffness or tingling which precedes pain and swelling	Synovial fluid from hemarthrosis typically does not clot

CPPD, calcium pyrophosphate disease; MSU, monosodium urate; WBC, white blood cell.

action, which includes the disruption of microtubule assembly, leukocyte activation, vacuolar movement, and cell migration. Diarrhea is a common adverse event and can complicate the hospital course of patients in critical care or can require additional investigation during hospitalization. Colchicine should be used cautiously in patients with liver disease, especially in those with jaundice.

4.3 Corticosteroids

Glucocorticoids are potent anti-inflammatory agents that inhibit the transcription of many inflammatory genes that have established roles in gout flares. The typical dose of prednisone is 30–35 mg/day for five days [30, 35]. Systemic corticosteroids such as prednisone are a safe choice for patients who cannot tolerate NSAIDs or colchicine but should be used with caution in those with uncontrolled hyperglycemia or infection.

Intraarticular corticosteroid injection is safe and highly effective in acute monoarticular gout and may be the treatment of choice in patients with contraindications to oral medications and nothing-per-oral patients. Dosage usually ranges between 20 and 60 mg for triamcinolone, depending on joint size. Physicians should exercise caution in patients with severe bleeding tendency, suspected concurrent joint infection, and prosthetic joints.

4.4 Adrenocorticotrophic hormone

Adrenocorticotrophic hormone (ACTH), a fascinating therapeutic option for hospitalized patients, has a direct anti-inflammatory effect mediated by stimulating melanocortin type 3 receptors in macrophages in a steroid-independent manner. The usual intramuscular ACTH dosage is 25–40 IU, and treatment may be repeated if clinically indicated [34]. In a retrospective study assessing the efficacy of ACTH in 33 hospitalized patients with gout flares and multiple comorbidities that precluded the use of NSAIDs and colchicine, Ritter *et al.* [40] found that 40 IU ACTH administered every eight hours with gradual tapering was highly effective, with a response rate of 97%. Another retrospective review of 181 patients with gout flares during hospitalization reported a response rate of 78% following intramuscular administration of 1 mg (100 IU) synthetic ACTH [41]. In that study, short-course ACTH was not associated with hypertension, edema, or mood changes.

4.5 IL-1 inhibitors

IL-1 inhibitors are effective in relieving the signs and symptoms of gout flares [42]. IL-1, which is secreted by MSU crystal-stimulated monocytes and macrophages, is one of the major mediators of inflammation in gout flares. Anti-IL1 biologics include the targeted antibody (canakinumab), the modified receptor (rilonacept), and the recombinant receptor antagonist (anakinra). IL1-directed therapy has several advantages including good tolerability and low rates of gastrointestinal, renal, and metabolic adverse events. IL-1-directed therapy may be particularly appropriate in patients with multiple comorbidities, including critically ill patients and those with refractory gout flare. In a study of hospitalized

patients with acute crystal-associated arthritis, including gout flares in 93% of the cases, anakinra treatment led to significantly improvement within four days after the first dose in 75% of the patients [43]. However, concurrent infection may be a contraindication for IL-1 inhibitor use.

Gout flares should be treated as early as possible. Treatment should aim for quick suppression of inflammation with adequate dosing of anti-inflammatory agents and should continue until the flare is resolved. Local ice therapy is also a safe and effective supplementary therapy for people with gout flares [44]. Current treatment options for gout flares according to recent recommendations are summarized in Table 3 (Ref. [29–31]).

5. Urate-lowering therapy---setting the right priorities

Three classes of drugs approved for lowering urate levels are xanthine oxidase inhibitors, uricosuric agents, and uricase agents. Allopurinol is the preferred first-line agent in most guidelines. Patients with two or more gout flares per year, those with tophi, and those with radiographic damage attributable to gout greatly benefit from ULT [29].

Stopping ongoing ULT during a gout flare is not recommended, because it can lead to a sudden change in serum urate levels, crystal shedding, and ultimately a gout flare [13, 38]. The same rationale can also be applied to the critical care setting, where patients are already exposed to numerous potential triggers of gout flares such as acute kidney injury, acute illness, and diuretics. Withdrawal of ongoing ULT may be an additional risk for in-hospital gout flares [45]. However, stopping ULT may be unavoidable in certain contexts where ULT is clearly contraindicated, such as severe liver injury or suspected major cutaneous drug reactions, particularly in patients treated with allopurinol.

Another common clinical scenario is the development of a gout flare in a patient who receives initial gout diagnosis during hospitalization. Concerns may arise when ULT is indicated but the gout flare has not yet subsided. Traditionally, ULT is initiated 2–4 weeks after flare resolution because of concerns regarding prolonged flare due to a rapid decrease in serum urate levels and remodeling of articular urate crystal deposits [28]. The current guidelines on the timing of ULT administration are conflicting [46]. Three small controlled studies reported that ULT (allopurinol or febuxostat) initiation during a gout flare in ambulatory settings did not prolong the flare or worsen its severity when compared with delayed initiation, as long as the patients received appropriate anti-inflammatory treatment for the gout flare [47–49]. However, no study has investigated ULT initiation during gout flares in inpatient settings.

In the critical care setting, it is important to also consider the general wellbeing of patient in the context of ULT initiation. For example, a patient with evolving acute kidney injury may not be suitable for immediate allopurinol initiation because the starting allopurinol dosage depends on estimated glomerular filtration rate [50]. In such cases, waiting until kidney function stabilization may be prudent before starting allopurinol to minimize the risk of adverse drug reactions. The recent guidelines recommend maximum starting allopurinol

TABLE 3. Summary of gout flare treatments according to the guidelines for the management of gout.

Recommendation	First-line therapy	Second-line therapy
EULAR 2016 [30]	Colchicine	
	NSAIDs	IL-1 inhibitor
	Corticosteroids (intraarticular or oral)	
BSR 2017 [31]	NSAIDs	Corticosteroids (oral, intramuscular)
	Colchicine	IL-1 inhibitor
	Corticosteroids (intraarticular)	
ACR 2020* [29]	Colchicine	
	NSAIDs	IL-1 inhibitor ACTH
	Corticosteroids (oral, intraarticular or intramuscular)	

*For Nothing-per-oral patients; Corticosteroids (intramuscular, intravenous, or intraarticular) over IL-1 inhibitors or ACTH. ACR, The American College of Rheumatology; ACTH, Adrenocorticotropic hormone; BSR, The British Society for Rheumatology; EULAR, The European League Against Rheumatism; IL-1, interleukin 1; NSAIDs, nonsteroidal anti-inflammatory drugs.

TABLE 4. Summary of urate-lowering agents according to existing recommendations for gout management.

Recommendation	EULAR 2016 [30]	BSR 2017 [31]	ACR 2020 [29]
Indication for ULT initiation	Recurrent flares, tophi, urate arthropathy, renal stones	Diagnosis of gout	Frequent flares (≥2 per year), tophi, radiographic damage attributable to gout
Commencement during acute phase	Not specified	Discouraged	Recommended
First-line ULT	Allopurinol	Allopurinol	Allopurinol
Second-line ULT	Febuxostat	Febuxostat	Febuxostat

ACR, The American College of Rheumatology; EULAR, The European League Against Rheumatism; BSR, The British Society for Rheumatology; ULT, uric acid-lowering therapy.

dosages of 100 and 50 mg/day in patients with normal kidney function and in those with a glomerular filtration rate below 60 mL/min/1.73 m², respectively [29]. Allopurinol should subsequently be escalated every 2–5 weeks at the outpatient clinic until a target serum urate level of <0.36 mmol/L is reached [51]. Allopurinol has been associated with severe cutaneous adverse reactions and allopurinol hypersensitivity syndrome (AHS). One of the risk factors for AHS is genetic factors associated with the *HLA-B*5801* allele [52]. The ACR guideline recommends testing *HLA-B*5801* before starting allopurinol for Southeast Asian descent (for example, Han-Chinese, Korean, Thai) and African-American individuals, who have a higher prevalence of *HLA-B*5801* [29].

Febuxostat is a potent second-line xanthine oxidase inhibitor, with a usual dosage ranging between 80 and 120 mg/day [53]. Febuxostat should be used with caution in patients with uncontrolled cardiovascular disease due to the increased risk for all-cause and cardiovascular mortality [54]. There is no dosage adjustment of febuxostat in mild to moderate renal impairment [estimated glomerular filtration rate (eGFR) 30–89 mL/min/1.73 m²], but for severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²), febuxostat should be used with caution and the dosage is not to exceed 40 mg/day [55]. Uricosuric agents such as probenecid should also be initiated with caution because patients in critical care are particularly vulnerable to potential adverse events, such as hepatitis, and drug interactions. In severe renal impairment (eGFR <30 mL/min/1.73 m²), uricosuric agents including

benzbromarone, probenecid and sulfapyrazone become less efficacious and therefore should be avoided [56].

Allopurinol and benzbromarone can increase the anticoagulant effects of warfarin, so the serum INR level should be closely monitored. Both allopurinol and febuxostat can increase the toxicity of azathioprine. Benzbromarone is an inhibitor of CYP2C9 and therefore should not be used in combination with fluconazole and rifampicin [56].

Unless contraindicated, patients on gout flare prophylaxis should continue treatment during admission to ensure protection against gout flares. For those who are initiated on ULT during hospitalization, concurrent prophylaxis, such as colchicine 0.6 mg/day, should be prescribed until the target serum urate is maintained for 3–6 months [29]. Table 4 (Ref. [29–31]) summarizes ULT regimens for the management of gout according to current recommendations.

6. Conclusions

Patients in the critical care setting are at increased risk of gout flares, possibly due to acute critical illness and presence of several potential triggers for gout flares. Diagnosis can be challenging because the clinical manifestations of a gout flare can easily be confused with systemic inflammation due to concomitant conditions. Treatment options for gout flares are often limited by comorbid conditions that preclude the use of first-line anti-inflammatory agents. Ongoing ULT should be continued during hospitalization unless otherwise contraindicated. Finally, the benefit of ULT initiation during hospital

admission remains unclear. Future studies on the management of gout flares should also focus on hospitalized patients who are an especially vulnerable population. Improved in-hospital gout management will potentially lead to fewer gout flares and better hospital outcomes.

AUTHOR CONTRIBUTIONS

PS conceived the paper, reviewed relevant literature and wrote the first draft of the manuscript. KJ conceived the paper and revised the manuscript draft for academic integrity. Both authors have reviewed and given approval to the submitted version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

- [1] Singh JA, Gaffo A. Gout epidemiology and comorbidities. *Seminars in Arthritis and Rheumatism*. 2020; 50: S11–S16.
- [2] Wright S, Chapman PT, Frampton C, O'Donnell JL, Raja R, Stamp LK. Management of Gout in a Hospital Setting: a Lost Opportunity. *The Journal of Rheumatology*. 2017; 44: 1493–1498.
- [3] Zleik N, Elfishawi MM, Kvirgic Z, Michet CJ, Crowson CS, Matteson EL, *et al.* Hospitalization Increases the Risk of Acute Arthritic Flares in Gout: a Population-based Study over 2 Decades. *The Journal of Rheumatology*. 2018; 45: 1188–1191.
- [4] Robinson PC, Kempe S, Tebbutt I, Roberts L. Epidemiology of inpatient gout in Australia and New Zealand: temporal trends, comorbidities and gout flare site. *International Journal of Rheumatic Diseases*. 2017; 20: 779–784.
- [5] Russell MD, Yates M, Bechman K, Rutherford AI, Subesinghe S, Lanyon P, *et al.* Rising Incidence of Acute Hospital Admissions due to Gout. *The Journal of Rheumatology*. 2020; 47: 619–623.
- [6] Fisher MC, Pillinger MH, Keenan RT. Inpatient gout: a review. *Current Rheumatology Reports*. 2014; 16: 458.
- [7] Jeong H, Jeon CH. Clinical characteristics and risk factors for gout flare during the postsurgical period. *Advances in Rheumatology*. 2019; 59: 31.
- [8] Shao BZ, Xu ZQ, Han BZ, Su DF, Liu C. NLRP3 inflammasome and its inhibitors: a review. *Frontiers in Pharmacology*. 2015; 6: 262.
- [9] Terkeltaub R. What makes gouty inflammation so variable? *BMC Medicine*. 2017; 15: 158.
- [10] Kang EH, Lee EY, Lee YJ, Song YW, Lee EB. Clinical features and risk factors of postsurgical gout. *Annals of the Rheumatic Diseases*. 2008; 67: 1271–1275.
- [11] Zhuo Y, Cai X, Hou Z, Zhu Z, Cai D. Postoperative Recurrent Gout Flares: A Cross-sectional Study From China. *Journal of Clinical Rheumatology*. 2020; 26: 197–203.
- [12] Lin Y, Hsu H, Huang Y, Lee M, Huang W, Huang Y, *et al.* Gouty Arthritis in Acute Cerebrovascular Disease. *Cerebrovascular Diseases*. 2009; 28: 391–396.
- [13] Jatuworapruk K, Grainger R, Dalbeth N, Taylor WJ. Development of a prediction model for inpatient gout flares in people with comorbid gout. *Annals of the Rheumatic Diseases*. 2019; 79: 418–423.
- [14] Richette P, Bardin T. Purine-rich foods: an innocent bystander of gout attacks? *Annals of the Rheumatic Diseases*. 2012; 71: 1435–1436.
- [15] Perez-Ruiz F, Castillo E, Chinchilla SP, Herrero-Beites AM. Clinical Manifestations and Diagnosis of Gout. *Rheumatic Disease Clinics of North America*. 2014; 40: 193–206.
- [16] Dalbeth N, Gosling AL, Gaffo A, Abhishek A. Gout. *The Lancet*. 2021; 397: 1843–1855.
- [17] Neogi T, Jansen TLTA, Dalbeth N, Fransen J, Schumacher HR, Berendsen D, *et al.* 2015 Gout classification criteria: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Annals of the Rheumatic Diseases*. 2015; 74: 1789–1798.
- [18] Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castaneda J, *et al.* 2018 updated European League against Rheumatism evidence-based recommendations for the diagnosis of gout. *Annals of the Rheumatic Diseases*. 2020; 79: 31–38.
- [19] Schlesinger N, Norquist JM, Watson DJ. Serum urate during acute gout. *The Journal of Rheumatology*. 2009; 36: 1287–1289.
- [20] Dalbeth N, Choi HK, Joosten LAB, Khanna PP, Matsuo H, Perez-Ruiz F, *et al.* Gout. *Nature Reviews Disease Primers*. 2019; 5: 69.
- [21] Pascart T, Liote F. Gout: state of the art after a decade of developments. *Rheumatology*. 2019; 58: 27–44.
- [22] Ogdie A, Taylor WJ, Neogi T, Fransen J, Jansen TL, Schumacher HR, *et al.* Performance of Ultrasound in the Diagnosis of Gout in a Multicenter Study: Comparison with Monosodium Urate Monohydrate Crystal Analysis as the Gold Standard. *Arthritis & Rheumatology*. 2017; 69: 429–438.
- [23] Chou H, Chin TY, Peh WCG. Dual-energy CT in gout - a review of current concepts and applications. *Journal of Medical Radiation Sciences*. 2017; 64: 41–51.
- [24] Bongartz T, Glazebrook KN, Kavros SJ, Murthy NS, Merry SP, Franz WB, *et al.* Dual-energy CT for the diagnosis of gout: an accuracy and diagnostic yield study. *Annals of the Rheumatic Diseases*. 2015; 74: 1072–1077.
- [25] Fam AG, Reis MD, Szalai JP. Acute gouty synovitis associated with “urate milk”. *Journal of Rheumatology*. 1997; 24: 2389–2393.
- [26] Shah K, Spear J, Nathanson LA, McCauley J, Edlow JA. Does the presence of crystal arthritis rule out septic arthritis? *The Journal of Emergency Medicine*. 2007; 32: 23–26.
- [27] Muangchan C, Bhurirun T. An investigation of the independent risk factors that differentiate gout from pseudogout in patients with crystal-induced acute arthritis: a cross-sectional study. *Rheumatology International*. 2018; 38: 89–95.
- [28] Neogi T. Clinical practice. Gout. *The New England Journal of Medicine*. 2011; 364: 443–452.
- [29] FitzGerald JD, Dalbeth N, Mikuls T, Brignardello-Petersen R, Guyatt G, Abeles AM, *et al.* 2020 American College of Rheumatology Guideline for the Management of Gout. *Arthritis Care & Research*. 2020; 72: 744–760.
- [30] Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castañeda-Sanabria J, *et al.* 2016 updated EULAR evidence-based recommendations for the management of gout. *Annals of the Rheumatic Diseases*. 2017; 76: 29–42.
- [31] Hui M, Carr A, Cameron S, Davenport G, Doherty M, Forrester H, *et al.* The British Society for Rheumatology Guideline for the Management of Gout. *Rheumatology*. 2017; 56: 1056–1059.
- [32] Billy CA, Lim RT, Ruospo M, Palmer SC, Strippoli GFM. Corticosteroid or Nonsteroidal Antiinflammatory Drugs for the Treatment of Acute Gout: a Systematic Review of Randomized Controlled Trials. *The Journal of Rheumatology*. 2018; 45: 128–136.
- [33] Roddy E, Clarkson K, Blagojevic-Bucknall M, Mehta R, Oppong R, Avery A, *et al.* Open-label randomised pragmatic trial (CONTACT) comparing naproxen and low-dose colchicine for the treatment of gout flares in primary care. *Annals of the Rheumatic Diseases*. 2020; 79: 276–284.

- [34] Khanna D, Khanna PP, Fitzgerald JD, Singh MK, Bae S, Neogi T, *et al.* 2012 American College of Rheumatology guidelines for management of gout. Part 2: therapy and antiinflammatory prophylaxis of acute gouty arthritis. *Arthritis Care & Research.* 2012; 64: 1447–1461.
- [35] Janssens HJ, Janssen M, van de Lisdonk EH, van Riel PL, van Weel C. Use of oral prednisolone or naproxen for the treatment of gout arthritis: a double-blind, randomised equivalence trial. *The Lancet.* 2008; 371: 1854–1860.
- [36] Rubin BR, Burton R, Navarra S, Antigua J, Londoño J, Pryhuber KG, *et al.* Efficacy and safety profile of treatment with etoricoxib 120 mg once daily compared with indomethacin 50 mg three times daily in acute gout: a randomized controlled trial. *Arthritis and Rheumatism.* 2004; 50: 598–606.
- [37] Terkeltaub RA, Furst DE, Bennett K, Kook KA, Crockett RS, Davis MW. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis and Rheumatism.* 2010; 62: 1060–1068.
- [38] Drug and Therapeutics Bulletin. Latest guidance on the management of gout. *British Medical Journal.* 2018; 362: k2893.
- [39] Estiverne C, Mount DB. The Management of Gout in Renal Disease. *Seminars in Nephrology.* 2020; 40: 600–613.
- [40] Ritter J, Kerr LD, Valeriano-Marcet J, Spiera H. ACTH revisited: effective treatment for acute crystal induced synovitis in patients with multiple medical problems. *The Journal of Rheumatology.* 1994; 21: 696–699.
- [41] Daoussis D, Antonopoulos I, Yiannopoulos G, Andonopoulos AP. ACTH as first line treatment for acute gout in 181 hospitalized patients. *Joint Bone Spine.* 2013; 80: 291–294.
- [42] So A, Dumusc A, Nasi S. The role of IL-1 in gout: from bench to bedside. *Rheumatology.* 2018; 57: i12–i19.
- [43] Liew JW, Gardner GC. Use of Anakinra in Hospitalized Patients with Crystal-associated Arthritis. *The Journal of Rheumatology.* 2019; 46: 1345–1349.
- [44] Schlesinger N, Detry MA, Holland BK, Baker DG, Beutler AM, Rull M, *et al.* Local ice therapy during bouts of acute gouty arthritis. *The Journal of Rheumatology.* 2002; 29: 331–334.
- [45] Jatuworapruk K, Grainger R, Dalbeth N, Lertnawapan R, Hanvivadhanakul P, Towiwat P, *et al.* The GOUT-36 prediction rule for inpatient gout flare in people with comorbid gout: derivation and external validation. *Rheumatology.* 2021. (in press)
- [46] Li Q, Li X, Wang J, Liu H, Kwong JS, Chen H, *et al.* Diagnosis and treatment for hyperuricemia and gout: a systematic review of clinical practice guidelines and consensus statements. *BMJ Open.* 2019; 9: e026677.
- [47] Hill EM, Sky K, Sit M, Collamer A, Higgs J. Does starting allopurinol prolong acute treated gout? A randomized clinical trial. *Journal of Clinical Rheumatology.* 2015; 21: 120–125.
- [48] Taylor TH, Mecchella JN, Larson RJ, Kerin KD, Mackenzie TA. Initiation of allopurinol at first medical contact for acute attacks of gout: a randomized clinical trial. *The American Journal of Medicine.* 2012; 125: 1126–1134.e7.
- [49] Sun R, Lu J, Li H, Cheng X, Xin Y, Li C. Evaluation of febuxostat initiation during an acute gout attack: a prospective, randomized clinical trial. *Joint Bone Spine.* 2020; 87: 461–466.
- [50] Stamp LK, Taylor WJ, Jones PB, Dockerty JL, Drake J, Frampton C, *et al.* Starting dose is a risk factor for allopurinol hypersensitivity syndrome: a proposed safe starting dose of allopurinol. *Arthritis and Rheumatism.* 2012; 64: 2529–2536.
- [51] Hanvivadhanakul P, Wongdet R. Outcome of Treatment in Gouty Arthritis Patients: a Retrospective Study. *Journal of the Medical Association of Thailand.* 2015; 98: S46–S50.
- [52] Stamp LK, Barclay ML. How to prevent allopurinol hypersensitivity reactions? *Rheumatology.* 2017; 57: i35–i41.
- [53] Lertnawapan R, Jatuworapruk K. Efficacy of febuxostat versus allopurinol and the predictors of achieving target serum urate in a cohort of Thai people with gout. *Clinical Rheumatology.* 2021; 40: 255–262.
- [54] White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, *et al.* Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout. *The New England Journal of Medicine.* 2018; 378: 1200–1210.
- [55] Juge P, Truchetet M, Pillebout E, Ottaviani S, Vigneau C, Loustau C, *et al.* Efficacy and safety of febuxostat in 73 gouty patients with stage 4/5 chronic kidney disease: a retrospective study of 10 centers. *Joint Bone Spine.* 2017; 84: 595–598.
- [56] Dalbeth N, Merriman TR, Stamp LK. Gout. *The Lancet.* 2016; 388: 2039–2052.

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