Things We Do for No Reason™: Discontinuing Urate-Lowering Therapy on Admission

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Inspired by the ABIM Foundation's Choosing Wisely® campaign, the "Things We Do for No Reason™" (TWDFNR) series reviews practices that have become common parts of hospital care but may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent clear-cut conclusions or clinical practice standards but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

CLINICAL SCENARIO

An infected diabetic foot ulcer requiring intravenous antibiotics prompts admission for a 58-year-old man with hypertension, insulin-dependent diabetes mellitus, gout, stage 3 chronic kidney disease (CKD), and hyperlipidemia. On admission, the hospitalist discontinued the patient's daily 300 mg of allopurinol, which had helped prevent a flare for more than 1 year. On day 3 of hospitalization, the patient developed right knee pain, swelling, and erythema. Due to concerns for septic arthritis, he underwent lab work, imaging, and joint aspiration, which confirmed the diagnosis of an acute gout flare. The prednisone he received for his gout flare caused hyperglycemia, requiring careful insulin titration during the remainder of his hospitalization.

BACKGROUND

Gout, the most common form of inflammatory arthritis, affects 3.9% of the US population. Its incidence has doubled in the past 2 decades, partly due to an increase in risk factors for gout, including obesity, diabetes, hypertension, hyperlipidemia, and renal disease.[1] Patients with gout incur high rates of hospitalization and costs related to the disease and its comorbidities.[2] Volume depletion, diuretic use, fluid shifts, or discontinuation of gout medications put patients at high risk of developing acute flares during hospitalization.[2-4]

Acute inflammatory response to monosodium urate crystal deposition in joints causes gout flares. Over time, uncontrolled gout leads to chronic inflammatory damage, causing permanent deformities and disability. Patients with uncontrolled gout have decreased work productivity and higher healthcare utilization and costs than patients with controlled gout.[5]

Gout treatment has two components: acute flare management and long-term therapy to lower serum uric acid levels. Patients with frequent gout attacks (≥two annually), tophi, or radiographic damage require urate-lowering therapy (ULT) to prevent further damage. Additionally, ULT is conditionally recommended for patients with their first flare and concomitant CKD stage 3 or higher, serum uric acid >9 mg/dL, or urolithiasis. First-line ULT incorporates xanthine oxidase inhibitors, such as allopurinol, due to efficacy and low cost.[6] Using a treat-to-target approach, allopurinol is titrated to achieve uric acid levels <6 mg/dL.[6,7] Controlling gout can take many months and requires careful medication titration, lifestyle modifications, and clear communication with patients. Poor adherence to ULT treatment complicates overall gout control and partly results from patients' and providers' knowledge gaps about gout and gout medications.[8,9] Prior studies demonstrated that poor adherence to ULT contributes to increased gout flares and resource utilization.[6,9]

WHY YOU MIGHT THINK STOPPING URATE-LOWERING THERAPY IS HELPFUL

In the authors' experience, hospitalists discontinue ULT for three reasons. First, hospitalists hold ULT, particularly allopurinol, when a patient has either acute or chronic kidney injury, due to concern that decreased excretion of drug metabolites increases the risk of allopurinol hypersensitivity syndrome (AHS) and allopurinol toxicity.[10] One small study reported a decrease or discontinuation of allopurinol in 21% of 73 admissions, citing concerns of using allopurinol in renal impairment.[10] Oxipurinol, a renally excreted metabolite of allopurinol, accumulates at higher concentrations in individuals with kidney impairment. The belief that elevated concentrations increase the risk of adverse effects has guided past recommendations about safety and dosing of allopurinol in patients with CKD.[11,12] Due to safety concerns, older guidelines and literature[11] suggest not increasing allopurinol more than 300 mg daily in patients with CKD.

Second, clinicians may want to stop "nonessential" medications on admission in order to simplify a medication list. If a patient's last gout flare occurred a long time ago, a clinician may think their gout no longer requires ULT.

Finally, ULT is discontinued during an acute gout flare because clinicians believe that continuing ULT will make flare symptoms worse. Allopurinol dissolves uric acid crystals, which can cause inflammation. The inflammation increases the risk

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of precipitating a gout flare when first starting allopurinol and during dose titration. Clinicians may feel that holding the medication during an acute flare avoids iatrogenesis that worsens the flare.

WHY STOPPING URATE-LOWERING THERAPY IS NOT HELPFUL

While physicians cite concerns of using allopurinol in renal impairment,[10] there are no absolute contraindications to allopurinol in kidney impairment. Clinicians can prescribe xanthine oxidase inhibitors to patients with moderate-to-severe CKD and can titrate allopurinol to doses greater than 300 mg daily safely in these same patients.[6,7,12-14] Prior studies sparked concern that poor allopurinol metabolite excretion in CKD might contribute to AHS or toxicity. However, more recent studies show that patients with CKD can take allopurinol safely, but that they require slower up-titration to mitigate the risk of flares and AHS. Guidelines recommend a starting dose of ≤100 mg of allopurinol in patients with normal renal function, and even lower doses in patients with CKD.[6] In studies showing safe dose titration in CKD, patients received an initial dose of allopurinol 50 mg daily, which increased by 50 mg every month.[13,14] When hospitalists abruptly stop ULT during hospitalization in patients with CKD, those patients have to restart from the initial low dose and up-titrate slowly back to the lowest dose that achieves serum uric acid <6 mg/dL.[6]

Acute kidney injury (AKI) is not an absolute contraindication to allopurinol use, and the scant amount of published literature does not support discontinuation. In this acute situation, a patient may require a dose reduction in allopurinol to avoid toxicity depending on the severity of AKI. A discussion with inpatient pharmacy can help find a safe dose based on current creatinine clearance.

Physicians anecdotally recognize ULT discontinuation as a cause of inpatient gout flares. Clinicians and patients should view ULT as essential, even in patients who remain symptom-free for years. Between acute flares, a patient enters a potentially asymptomatic phase called "intercritical gout" that varies in duration. Urate deposition causing tophi and damage still occur during this phase, so patients must continue on ULT even if they have no recent flare history.

ULT that appears on any outpatient medication list needs verification of dose and compliance before ordering. If a patient is actually taking a lower dose than listed or not taking ULT at all, starting at a higher dose puts them at risk for flare and AHS, especially in patients with renal disease. Continuing ULT during hospitalization after verifying dose and compliance can potentially prevent gout flares and their downstream effects, including increased costs and potential side effects from additional pain medications.

Patients on chronic ULT should continue it during an acute gout flare.[6,7] Literature and guidelines do not suggest that continuing ULT significantly worsens the intensity or duration of a flare. The initiation or up-titration of ULT, not the continuation of it, causes uric acid to dissolve, triggering an inflammatory response that increases the risk of gout flare. Therefore, guidelines recommend giving flare prophylaxis simultaneously for at least 3 to 6 months to prevent flares while starting and titrating ULT. Flare prophylaxis may continue longer depending on when a patient reaches a stable dose of ULT.[6,7] While patients are receiving acute flare treatment, continuing ULT will help lower their serum uric acid levels over time.

To emphasize the importance of treating gout with ULT even further, the most recent American College of Rheumatology gout management guidelines conditionally recommend starting ULT during an acute flare for increased adherence. Small studies have shown that initiation of ULT does not precipitate attacks or significantly increase duration of flare. Input from patients influenced this recommendation, as they felt highly motivated to start ULT during acute flare due to symptoms.[6]

Additionally, due to comorbidities, inpatients often cannot tolerate standard flare therapies, such as nonsteroidal anti-inflammatory drugs, corticosteroids, or oral colchicine, to treat their acute symptoms. Moreover, patients often have other analgesics, such as opiates, prescribed for pain control. During an acute flare, hospitalists will likely need to add medications to treat the acute symptoms, but ULT should be considered an essential medication and continued as well.

WHEN STOPPING URATE-LOWERING THERAPY MIGHT BE HELPFUL

Allopurinol can cause mild-to-severe cutaneous adverse reactions. AHS, a rare reaction that causes significant morbidity and mortality, presents with a rash, eosinophilia, fever, hepatitis, and progressive kidney failure. Risk factors for developing AHS include kidney impairment, higher starting doses, concurrent diuretic use, and presence of the genetic marker HLA B*5801.[12] AHS usually occurs in the first 8 weeks of initiation of allopurinol, but can occur later in treatment, especially in those with risk factors—notably kidney impairment.[12] When a patient on allopurinol develops a rash, the clinician should consider stopping allopurinol if concerned about AHS or, in milder cases, decrease the dose until the rash resolves.

WHAT YOU SHOULD DO INSTEAD

When you see ULT on a patient's medication list, verify the dose with the patient and continue it (even during an acute gout flare) unless a new rash has developed, or you are concerned about a drug-drug interaction. If a patient has a significant AKI, consider discussing dose modifications with your inpatient pharmacist.

RECOMMENDATIONS

- Consider ULT an essential medication and continue it during the hospitalization of a patient with a history of gout.
- Continue ULT while treating an acute gout flare.
- Continue ULT in patients with AKI and CKD, but discuss dose modifications with a pharmacist for AKI patients.

CONCLUSION

In the clinical scenario, the hospitalist did not treat ULT as an essential medication on admission, and the patient's gout

flared, leading to increased morbidity, resource utilization, and cost of hospitalization. Stopping ULT has downstream effects after discharge, including delays in achieving prior gout control. If ULT is discontinued, outpatient clinicians must restart it at lower doses and then up-titrate slowly, increasing the risk of flares and possibly contributing to nonadherence. During hospitalization, clinicians should continue ULT.

Do you think this is a low-value practice? Is this truly a "Thing We Do for No Reason™"? Share what you do in your practice and join in the conversation online by retweeting it on Twitter (#TWDFNR) and liking it on Facebook. We invite you to propose ideas for other "Things We Do for No Reason™" topics by emailing TWDFNR@hospitalmedicine.org

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