Allopurinol hypersensitivity syndrome: Raising awareness of an uncommon but potentially serious adverse event among kidney stone patients

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ABSTRACT

Allopurinol is a commonly prescribed agent in the urologic population for the prevention of urinary stones. Although generally well-tolerated, several serious potential side effects can occur with its use. Allopurinol hypersensitivity syndrome (AHS), in particular, is a relatively rare but potentially life-threatening complication. With the observed increase in urinary stone disease, especially those of uric acid composition, it is likely that the use of allopurinol will increase. Urologists play an important role in the assessment and medical management of patients with urinary stones, thus a greater awareness of the potential adverse events associated with allopurinol use, especially AHS, is important, as well as strategies that can minimize such risks. In this report we review the potential adverse effects of allopurinol. In addition, the results of a comprehensive review of the current literature on AHS will be presented, highlighting those patients at highest risk, reviewing the genetic susceptibility testing currently available, and providing guidance on best practices when allopurinol therapy is being considered.

KEY MESSAGES

- Uric acid stone disease is increasing in prevalence.
- Allopurinol is commonly prescribed for patients with hyperuricemia and uric acid stones, as well those with hyperuricemia/hyperuricosuria and calcium oxalate stones
- Allopurinol can be associated with severe complications, with a heightened risk associated with certain ethnicity and medical comorbidities.
- Susceptibility testing for HLA-B*58:01 is now available to screen patients at higher risk of allopurinol hypersensitivity syndrome

INTRODUCTION

Urolithiasis is a common condition with an increasing incidence over the past several decades, associated with significant morbidity.[1] In the U.S, it is estimated that approximately 10% of the general population will develop stone disease in their lifetime.[1] Among the various kidney stone types, uric acid nephrolithiasis accounts for 8%-10% of kidney stones world-wide and appears to be increasing in prevalence.[1,2] In the US, from the years 1980-2010, uric acid stone incidence doubled from 7-14%.[1]

Recurrent stone episodes are also very common among uric acid stone formers and may be as high as 32% within two years.[3] Prevention is therefore an important aspect in the care of these patients. Several urological clinical practice guidelines recommend performing an in-depth metabolic evaluation in high-risk stone formers, such as patients with uric acid stone composition, to guide medical preventative strategies.[4-6] Uric acid stones may form as the result of several underlying systemic disorders including obesity, metabolic syndrome, diabetes mellitus, gout, excessive bicarbonate loss due to high output bowel disease, myeloproliferative disorders, and tumor lysis syndrome.[5] As such, various metabolic abnormalities can be uncovered in patients with uric acid stones. Most commonly uric acid stone formation is associated with low urinary pH and low urine volumes rather than hyperuricemia or hyperuricosuria.[7] Accordingly, stone prevention is usually initially directed toward alkalinizing the urine pH to above 5.5 and increasing fluid intake to raise urine volumes.[8] When hyperuricemia is found, xanthine oxidase inhibitors such as allopurinol and febuxostat can be used as adjunctive therapy in patients when attempts at dietary purine restriction are unsuccessful.[5]

Metabolic evaluation is also indicated for patients with recurrent calcium oxalate stones, and a variety of risk factors may be uncovered including hyperuricosuria and/or hyperuricemia. Allopurinol is an approved second line therapy for treating calcium oxalate stones in the setting of documented hyperuricosuria and/or hyperuricemia.[4]

Allopurinol is an analogue of the purine hypoxanthine and is metabolized in the liver to its active metabolite, oxypurinol.[9] Both compounds are renally excreted. Allopurinol has a half-life of 1-2 hours, whereas oxypurinol's is approximately 15 hours.[9] The mechanism of action of allopurinol and its metabolite is through the inhibition of the xanthine oxidase enzyme, thereby preventing the conversion of xanthine to uric acid and lowering serum uric acid levels.[10] For the treatment of patients with gout and hyperuricemia who have normal renal function, the American College of Rheumatology recommends starting allopurinol at 100 mg/day and titrating the dose upward to a maximum of 800 mg/day to achieve serum uric acid levels of less than 6 mg/dl.[11] For patients with renal impairment (chronic kidney disease stage IV or greater) a starting dose of 50 mg/day is recommended.[12] In the prevention of urinary stones the recommended Allopurinol dose is 200-300 mg/day.[5]

There are several potential drug interactions to be aware of when considering prescribing allopurinol. Both azathioprine and 6-mercaptopurine are metabolized by xanthine oxidase, and

concomitant use of these with a xanthine oxidase inhibitor such as allopurinol can lead to agranulocytosis and pancytopenia.[9] Although generally well-tolerated, allopurinol use is associated with several adverse effects, ranging from those that are relatively minor to potentially life-threatening conditions. Minor side effects include maculopapular rash, as well as nausea and diarrhea.[13] Other rare adverse events include hepatitis, liver necrosis, cholestatic jaundice and interstitial nephritis. Laboratory abnormalities have also been noted including elevation of liver enzymes, thrombocytopenia, and leukopenia.[13]

The most serious adverse event is the development of Allopurinol Hypersensitivity Syndrome (AHS) which includes Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and eosinophilia with systemic symptoms.[14] AHS was first reported by Lang in 1979, and diagnostic criteria were established in 1986 (Table 1).[15,16] The condition is categorized as a severe cutaneous adverse reaction (SCAR).[17]

AHS has been reported to affect 1 in 1000 patients prescribed allopurinol, and is believed to be an idiosyncratic manifestation of a cell-mediated hypersensitivity reaction.[11,18] Patients of Korean, Han Chinese, and Thai ethnicity are also at heightened risk of AHS related to a genetic susceptibility.[19-22] While uncommon, AHS is associated with a mortality rate as high as 28% especially when SJS and TEN develop.[11,23] With the development of AHS, end organ injury can occur including hepatic dysfunction, acute kidney injury, as well as cardiac and pulmonary manifestations.[10] Of note, the effects can be transient if the condition is caught early, with cessation of allopurinol and prompt supportive care.[10]

Although several other pharmacological agents have been associated with the development of SJS and TEN, allopurinol has become the most common drug-induced cause.[23] With an increasing number of patients afflicted with uric acid stone disease, it seems likely that allopurinol prescribing will further increase. A thorough understanding of the risks associated with its use and potential mitigation strategies, especially for those patients at a heightened risk of an adverse drug event, is important to counsel patients adequately before prescribing allopurinol. In this article we will review the current state of knowledge of AHS. Focus will be made on identifying patients at heightened risk of developing the condition, the currently available genetic susceptibility testing, and strategies to mitigate the risk of AHS.

METHODS

We performed a literature review using PubMed, Embase, and Medline databases from January 1990 to July 2023. Search criteria included the terms: “allopurinol hypersensitivity”,” “drug hypersensitivity reactions”, “diagnostic utility of *HLA-B*58:01*”, “treatment of hyperuricemia with uric acid stones”, and the “cost effectiveness of *HLA-B*58:01* testing”. Only manuscripts published in the English-speaking literature were included, and all meeting abstracts were excluded.

All articles obtained from the literature review were analyzed regarding the types of drug hypersensitivity reactions documented from allopurinol usage and that fit the diagnostic criteria as outlined by Singer and Wallace.[16] From this review we attempted to ascertain the current

prevalence of AHS, and to identify those patients at the highest risk. The availability and cost-effectiveness of implementing screening for *HLA-B*58:01* was also evaluated.

RESULTS

A systematic review published by Ramasamy et al in 2019 analyzed the literature between 1950-2012 and identified a cohort of 802 patients who met the criteria for AHS.[10] Among this group, allopurinol dosing was only known for 339 (42.3%) patients and ranged from 100 to greater than 500 mg/day. Males were slightly more commonly afflicted (57.6%) compared to females (42.4%). The mean age of affected patients was 59.8 years of age. Most patients developed cutaneous skin manifestations 787 (98%) and of these, 48% of them went onto develop SJS/TEN. Prodromal signs and symptoms were commonly present and included fever, sore throat, fatigue, chills, nausea, and diarrhea. A portion of this cohort showed biochemical eosinophilia (22.7%) and/or leukocytosis (31.2%). The mortality rate reported for patients who developed AHS was 14% in this series.[10] This mortality rate was less than other reports[11, 23] and may reflect variable pre-existing patient co-morbidities and different rates of SJS/TEN between the cohorts.

The highest risk for AHS was noted within the first few months of therapy initiation, with the onset most commonly occurring at a mean of 10 weeks after starting allopurinol. Documented cases were seen however, as early as the first week after beginning therapy.[10] The review also confirmed concomitant medical illnesses that have been associated with AHS occurrence. Pre-existing renal disease was identified most commonly in 48.4% of patients, followed by hypertension (42.5%), type II diabetes mellitus (11.7%), malignancy (10.4%) and chronic heart failure (7.7%). Renal insufficiency, specifically chronic kidney disease stage III or higher, is known to reduce the excretion of allopurinol and its active metabolite oxypurinol thereby increasing the risk of AHS. This finding is supported by Chung et al who found persistently elevated plasma levels of the metabolite oxypurinol among patients who developed AHS, which also correlated with a poor prognosis for recovery.[24] Other observed risk factors included higher starting doses of allopurinol and concomitant use of diuretic medications especially thiazides.[9] In the systematic review of 802 patients who developed AHS, when the dose of allopurinol was available in the setting of impaired renal function, 85% of the patients had received a higher than recommended daily dose.[10] This re-confirms the importance of renal insufficiency and high doses of allopurinol as risk factors for the development of AHS.

In the systematic review, the majority of affected AHS patients were of East Asian background, involving 73% of the cohort. In a subgroup analysis, it was found that patients from Taiwan were the most common group at risk, representing 36% of all patients affected. AHS was significantly less commonly observed in those of European (14.1%), African (6.8%), American (5.3%) and Oceanic (1.0%) origin.[10] This susceptibility appears to be genetic and has been linked to Human Leukocyte Antigen B (HLA)-B which has an important role in the immune system's response to pathogens.[25] The variant *HLA-B*58:01* allele is associated with severe skin reactions among patients taking allopurinol and is most commonly found among the Asian populations

mentioned above.[11] The allele is considered co-dominant meaning having one copy of the allele is sufficient to put a patient at risk. Among patients included in the systematic review, *HLA-B*58:01* genotyping was performed in 166 (20.7%) patients.[10] One hundred and forty-six patients (18.2%) were positive for the variant allele and were of Chinese Han descent, while the remaining 20 (2.5%) were of European heritage.

Hershfield et al on behalf of the Clinical Pharmacogenetics Implementation Consortium (CPIC) produced guidelines on allopurinol dosing and *HLA-B*58:01*genotype testing in 2013.[25] Several ethnic populations were studied to develop the guideline. Among a Taiwanese population that were of Han-Chinese descent, the *HLA-B*58:01* allele was present in 100% of the patients (51/51) that developed SCAR while on allopurinol, compared to only 15% of patients (20/135) who were allopurinol tolerant, and 20% of patients (19/93) in the general population not on allopurinol. Comparatively, CPIC reviewed data from Japan where 56% of patients (10/18) that developed AHS had a positive *HLA-B*58:01* variant, and a general population control rate of 0.1% (6/493 patients) *HLA-B*58:01* positivity. In Korea, the prevalence of the HLA-B variant in patients diagnosed with AHS was 80% (4/5 patients) compared to a population control showing a prevalence of 12% (59/485 patients). In Thailand, the prevalence of *HLA-B*58:01* positivity in patients diagnosed with AHS was 100% (25/25 patients) versus the population control of only 13% (7/54 patients). Lastly, among France's population the *HLA-B*58:01* prevalence in AHS affected individuals was 55% (15/27 patients) and only 1.5% in controls (28/1822 patients).[16]

From the CPIC review it was recommended that in high-risk groups such as the Han-Chinese population, HLA testing should be performed before starting allopurinol.[25] In the setting of a positive *HLA-B*58:01* test, it was suggested that allopurinol should be avoided, and an alternative medication be considered. A summary of *HLA-B*58:01* allele positivity in different ethnic groups is presented in table 2.

Despite the pre-administration screening recommendation, a recent Canadian study based on a dermatology consult service database demonstrated that the use of *HLA-B*58:01* screening for allopurinol hypersensitivity was underutilized in an east Asian ethnic population.[26]

In 2015, the CPIC carried out an updated literature review and searched for other possible HLA alleles that may be associated with a risk of AHS.[27] A total of 12 studies showed a possible correlation with the alleles *HLA-A 33:03* and *HLA-03:02*. This association, however, was not strong enough to warrant inclusion in the updated CPIC guidelines, and it was reaffirmed that *HLA-B*58:01* is the only known allele strongly associated with AHS at this time.

In collaboration with the American College of Rheumatology, it has been recommended that *HLA-B*58:01* testing be performed prior to the initiation of allopurinol in populations that are at high risk of AHS including individuals of Korean ethnicity with stage 3 kidney disease or worse, and patients of Thai or Han Chinese ancestry.[11] The guideline also emphasized that negative *HLA-B*58:01* testing does not eliminate the possibility of a severe cutaneous reaction

especially in the European population. A summary of the American College of Rheumatology guidelines for initiating allopurinol therapy are presented in table 3.[11]

DISCUSSION

It is currently estimated that 10% of the general population has hyperuricemia, and with the increasing prevalence of obesity and metabolic syndrome this prevalence is likely to increase.[28] The impact of this observation for urology patients is that uric acid stone disease is on the rise. In patients being considered for allopurinol medical prophylaxis, awareness of the HLA-B allele status may guide clinicians in determining the safety of allopurinol use and lower the likelihood of serious side effects. Based on the current literature, it has been suggested that for those populations with a greater than 5% risk of *HLA-B*58:01* allele frequency, genotyping should be considered before allopurinol use.[23] Jutkowitz et al. determined the cost-effectiveness of universal polymerase chain reaction (PCR) *HLA-B*58:01* testing before starting allopurinol compared to no testing in a U.S. population.[28] In their study, costs, quality-adjusted life years, and incremental cost-effectiveness ratios were estimated over a lifetime. *HLA-B*58:01* screening was considered cost-effective for populations of African American and Asian descent but not for those of Caucasian or Hispanic ancestry.

In Canada, *HLA-B*58:01* testing is not yet universally available. In an on-line review of the provincial and territorial ministries of health and private laboratory websites, testing is available in British Columbia, Alberta, Ontario and Quebec through hospital and/or private laboratories, but not accessible in the other provinces. This may represent an opportunity for the Canadian Urological Association, the Canadian Society of Nephrology and other patient-focused organizations to aid in advocacy efforts to make access to testing more equitable across the country. Where testing is available results generally are reported within 14 days.

If testing is available and a patient is found to have the *HLA-B*58:01* allele, allopurinol should not be prescribed and alternative medical therapy should be considered.[29] Allopurinol desensitization utilizing a very low starting dose and gradually increasing over several weeks has been described for patients who have had minor skin reactions; however, these protocols are not recommended for patients who have had more serious reactions such as AHS.[30,31]

If a patient is considered at high risk of AHS, is unable to take allopurinol due to other side effects, or has severe renal impairment an alternative agent to consider is febuxostat. Febuxostat is a nonpurine selective inhibitor of both the oxidized and reduced forms of xanthine oxidase and, was approved in February 2009 by the US Food and Drug Administration (FDA) for the management of hyperuricemia in adults with gout. This agent has also been studied in the stone patient population and found to be more effective in lowering 24 hour uric acid levels compared to allopurinol or placebo.[32] Febuxostat does not require dosage adjustment in patients with mild to moderate renal impairment (creatinine clearance, 30-89 mL/min). There are no studies that have identified any cross reactivity to allopurinol, however, there have been case reports of febuxostat hypersensitivity when febuxostat was introduced due to a history of AHS especially in those patients with chronic kidney disease[33]. It should also be noted however, that

the FDA has issued a Black Box Warning, their highest-level alert, regarding the higher risk of cardiovascular death and death from all causes associated with febuxostat compared to allopurinol.[34] As such the FDA recommends febuxostat only for those patients who have failed, do not tolerate, or are unable to take allopurinol.

CONCLUSIONS

AHS is a rare but potentially serious complication associated with allopurinol use. With increasing rates of uric acid stone occurrence, it is conceivable that urologist prescribing of allopurinol will increase, putting more patients at risk of this rare but life-threatening adverse event. Understanding patient risk factors, and the incorporation of currently available genetic susceptibility testing based on current guidelines before starting therapy may aid in reducing the risk.

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FIGURES AND TABLES

Table 1. Diagnostic criteria of allopurinol hypersensitivity syndrome[16]
1) Exposure to allopurinol
2) Lack of exposure to another drug likely to cause a similar clinical picture
3) Clinical picture (either 2 major OR 1 major and 1 minor criteria)
a) Major criteria
i) Worsening renal function
ii) Acute hepatocellular injury
iii) Rash
(1) Diffuse maculopapular rash
(2) Exfoliative dermatitis
(3) Erythema multiforme
(4) Toxic epidermal necrolysis
b) Minor criteria
i) Fever
ii) Eosinophilia
iii) Leukocytosis

Table 2. Frequencies of *HLA-B*58:01* allele positivity reported for various ethnic groups		
Ethnic group	**Average HLA-B*58:01 carrier frequency (%) (Hershfield et al)[25]**	**Average HLA-B*58:01 carrier frequency (%) (Jutkowski et al)[28]**
Asian	6.1	7.4
African American	4.3	3.8
Caucasian	0.75	<1
Hispanic	1.2	<1
Middle Eastern	3.7	–

Table 3. American College of Rheumatology Guidelines for treatment of hyperuricemia with allopurinol[11]
• Prior to initiation, consider *HLA-B*58:01* in patients at higher risk for AHS
○ Korean descent with stage III or worse CKD
○ Han Chinese descent
○ Thai descent
• Starting dose no greater than 100 mg/day
• If stage IV CKD or higher start at 50 mg/day
• Gradually titrate dose upwards every 2–5 weeks to appropriate maximum dose to target serum uric acid level
• Educate patient on monitoring for drug toxicity including pruritis and rash

AHS: allopurinol hypersensitivity syndrome; CKD: chronic kidney disease.