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# The pattern of allopurinol prescription in a university hospital practice

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## Abstract

**Background:** Allopurinol as a drug is commonly used to treat gout and its complications. The aim usually is to lower the level of serum uric acid. Also, it was found to be prescribed in cases of asymptomatic hyperuricemia. However, this medication has serious side effects and some of these are fatal. So the aim of the current research work is to look at its use, whether properly indicated or not, in a university hospital.

**Results:** A total of 427 patients were included in this study. Only 3.7% (16) of the patients had the drug for significant hyperuricemia. Gout was confirmed in 40 (9.4%) patients.

**Conclusion:** It is clear that most patients received allopurinol without proper indications. The inappropriate use of allopurinol should be looked at to reduce the cost of medication and more importantly to avoid possible adverse effects.

**Keywords:** Allopurinol, Uric acid, Hyperuricemia, Gout

## Background

Allopurinol is a drug that is widely used by more than 1.2 million patients in the USA and UK [1]. It is prescribed for patients with uric acid deposition disorders such as gouty arthritis, uric acid stones, and recurrent calcium oxalate kidney stones [2–4] and tumor lysis syndrome [5].

It is a xanthine oxidase inhibitor which inhibits the enzyme that is responsible for the conversion of hypoxanthine to xanthine and xanthine to uric acid, hence decreased uric acid production [6]. It is used as a uric acid-lowering agent started after incidental finding of this desirable side effect during a trial as an adjuvant therapy for leukemia [7].

One of the most common reasons for its prescription is asymptomatic hyperuricemia, which is defined as a serum uric acid level greater than 7.0 mg/dl, as measured

by the automated enzymatic (uricase) method. It is very common in the population reaching up to 25% in males and 15% in females [8]. Most of the patients with hyperuricemia will continue as asymptomatic hyperuricemia and will not develop any of the uric acid deposition disorders [6].

As hyperuricemia itself is not a disease but merely a risk factor, therefore starting treatment in this group of patients is still controversial.

To confirm gout diagnosis, urate crystals should be seen in smear. Morphology of monosodium urate crystals is preserved in cytology and can be diagnosed with confidence by the pathologist on cytological analysis [9].

Recently, ultrasound has been shown to be a new promising imaging modality for the diagnosis of the gout [10]. Advantages are being non-invasive, lack of radiation, non-expensive, high resolution, and can be used as a guide for minimally invasive procedures [11].

The present study was conducted to discover the improper use of allopurinol in a university hospital.

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## Methods

A computer search using pharmacy data in KHUH, for all adults who received allopurinol from January 1, 2016, to January 1, 2017, was carried out. The list of patient IDs was taken from the hospital pharmacy system for all the available generic names and doses (loric and no uric, 100 mg and 300 mg for both). Patient demographic data and laboratory results were taken from patients' electronic files in the hospital system.

In addition to demographic data, clinical diagnosis for which allopurinol was given, dosage, renal disease and its stage, as well as complications of the drug, were collected from the medical records. The diagnosis of gout was made according to criteria of American college of Rheumatology [12]. Only patients less than 18 years were excluded.

## Statistical analysis

All data were analyzed using software program Statistical Package for Social Science (SPSS version 25). Descriptive statistics (mean percentage, and standard deviation) for continuous variables were calculated and frequencies were determined for categorical variables.

## Results

A total of 427 patients who were prescribed allopurinol from January 1, 2016, to January 1, 2017, were studied. This report includes 297 (69.6%) males and 130 females (30.41%) (Table 1). The mean  $\pm$  SD age was 60.80  $\pm$  15.030 years. Grouping age was conducted by decade. Approximately half of the patients sampled (49.4%) were distributed among ages 50 and 70 years (Table 2).

Table 3 reports the percentage of chronic kidney disease (CKD) patients divided by stages. Overall, 13.3% of patients did not have chronic kidney disease (CKD) (57 patients), while the remaining patients sampled had CKD, who were distributed among stages following the classification reported by Levey et al. [13]. The largest sampled groups were in stages 2 and 3 (28.8% and 29.7% for stage 2 and stage 3, respectively). Table 4 reports the percentage of indications for allopurinol prescription. Overall, 7.7% (33 patients) had allopurinol without a valid indication to use it

The percentage of patients who were taking allopurinol for kidney stone without analysis done to the stone

**Table 1** Frequency and percentage of study population divided by gender

	Frequency	Percent	Valid percent	Cumulative percent
Valid				
Male	297	69.6%	69.6%	69.6%
Female	130	30.4%	30.4%	100.0%
Total	427	100.0%	100.0%	

**Table 2** Age group of study population classified by decade

	Frequency	Percent	Valid percent	Cumulative percent
20 < age $\leq$ 30	13	3.0%	3.0%	3.3%
30 < age $\leq$ 40	29	6.8%	6.8%	9.8%
40 < age $\leq$ 50	58	13.6%	13.6%	23.4%
50 < age $\leq$ 60	108	25.3%	25.3%	48.7%
60 < age $\leq$ 70	103	24.1%	24.1%	72.8%
70 < age $\leq$ 80	66	15.5%	15.5%	88.3%
80 < age $\leq$ 90	25	5.9%	5.9%	94.1%
Age > 90	9	2.1%	2.1%	96.3%
Patients died at certain age	16	3.7%	3.7%	100.0%
Total	427	100.0%	100.0%	

was 12.9% (55 patients), while 1.4% (6 patients) had a uric acid stone. Confirmed gout was reported in 9.4% (40 patients) while 11.7% (50 patients) had gout but not confirmed. 1.9% and 0.5% of patients received allopurinol for recurrent calcium oxalate stone and hemolysis, respectively.

On the contrary, ~ 3.7% of patients (16 patients) were prescribed allopurinol for significant hyperuricemia (Table 5). Review of patients' files did not show cases experiencing allopurinol adverse effects.

## Discussion

Although allopurinol is a well-tolerated medication, it has many side effects that range from mild gastric upset or minimal rash to severe life-threatening conditions, such as Steven Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), allopurinol hypersensitivity syndrome, and drug rash with eosinophilia and systemic symptoms (DRESS syndrome) [14–16]. Allopurinol hypersensitivity syndrome approximately accounts for 0.4% of the new

**Table 3** Frequency and percentage of chronic kidney disease (CKD) patients divided by stages

	Frequency	Percent	Valid percent	Cumulative percent
Stage 1	30	7.0%	7.2%	7.2%
Stage 2	123	28.8%	29.4%	36.5%
Stage 3	127	29.7%	30.3%	66.8%
Stage 4	59	13.8%	14.1%	80.9%
Stage 5 no HD	17	4.0%	4.1%	85.0%
Stage 5 with HD	6	1.4%	1.4%	86.4%
No CKD	57	13.3%	13.6%	100.0%
Total	419	98.1%	100.0%	
Missing	8	1.9%		
Total	427	100.0%		

CKD chronic kidney disease

**Table 4** Distribution of study population according to the indications of allopurinol prescription

Indication	Frequency	Percent	Valid percent	Cumulative percent
None	32	7.5%	7.5%	7.5%
Gouty arthritis (confirmed)	40	9.4%	9.4%	16.9%
Gouty arthritis (not confirmed)	50	11.7%	11.7%	28.6%
Marked hyperuricemia (13 male, 10 female)	19	4.4%	4.5%	33.1%
Insignificant hyperuricemia (less than 13 males, 10 females)	208	48.7%	48.8%	81.9%
Kidney stone (was not analyzed)	55	12.9%	12.9%	94.8%
Uric acid stone	6	1.4%	1.4%	96.2%
Recurrent calcium oxalate stone	8	1.9%	1.9%	98.1%
Hemolysis (regardless of the cause)	2	0.5%	0.5%	98.6%
Genetic defects	3	0.7%	0.7%	99.3%
Malignancy	3	0.7%	0.7%	100.0%
Total	426	99.8%	100.0%	
Total	427	100.0%		

patients who are using it. Allopurinol was the most common cause of SJS and TEN in Europe and Israel with 17.4% of the cases [17]. These diseases can be fatal as the mortality rates for SJS and TEN are ~ 30% [18] and it is 18–32% for allopurinol hypersensitivity syndrome [14].

The inappropriate prescription of allopurinol has been described in the literature in some studies with small numbers. In a review of the 59 patients who were diagnosed with allopurinol hypersensitivity, only 13.5% were given the drug for appropriate reasons and 8 patients had severe disease that lead to death [19]; in another study done in Brooklyn of 8 patients, only 1 patient had an appropriate indication for allopurinol and 3 of them died as a complication of allopurinol hyposensitivity [19]. One study in Singapore involved 28 patients with mortality of 18% and the indicated prescription was only 36%. A report from Thailand showed 46.9% of the prescriptions were not appropriate [20]. In a study done in Saudi Arabia in Taif, the percentage of indicated prescription was only 13.5% out of 156 patients [21].

Hyperuricemia is a condition frequently met in clinical practice; in spite of the degree of hyperuricemia correlates with development of gout, almost 70% of patients with hyperuricemia never proved to develop gout up to 30 years of follow-up [22]. So the majority of patients

with hyperuricemia are not in need of hyperuricemia drug unless indicated clinically.

There are three conditions for asymptomatic hyperuricemia to be treated with allopurinol: (1) in presence of persistent uric acid levels above 13 mg/dL in men or 10 mg/dL in women, (2) in the presence of urinary excretion of uric acid exceeding 1100 mg/day, and (3) in patients about to receive radiation or chemotherapy [1]. Results of our research showed that 187 (43.79%) received allopurinol without justification for hyperuricemia.

In our review, 90 patients had allopurinol prescribed for diagnosis of gout; however, the disease was confirmed only in 40 patients.

Patients with acute arthritis and hyperuricemia do not always have gout. The diagnosis of the disease requires identification of monosodium urate crystals in synovial fluid of an acute inflamed joint. If this cannot be reached, diagnosis of gout can be confirmed by the diagnostic criteria developed by American College of Rheumatology in 2015 [12].

Over the past years, new interest was shown in the use of ultrasound in diagnosis of gout. The disease can be diagnosed by detecting hyperechoic articular surface features on the hyaline cartilage (double contour sign or DCS). Snowstorm appearance is suggestive of floating hyperechoic monosodium urate crystals or hyperechoic aggregation within the joint or along the tendons could indicate tophi [10]. Ultrasonography may help in the differential diagnosis of acute arthritis when special microscopic technical experience is not available [23].

Patients with a history of kidney stones who are at risk for recurrent uric acid nephrolithiasis should be considered for long-term allopurinol treatment [6, 24]. Another link between allopurinol therapy and kidney disease is the claim that lowering uric acid level may

**Table 5** Uric acid level at first prescription

	Frequency	Percentage
Marked hyperuricemia	16	3.7
Insignificant hyperuricemia	187	43.79
Normal levels	154	36.01
Missing	70	16.39
Total	427	100

decrease progression of renal failure and degree of hypertension [25]. However, our study showed that 55 patients (12.9%) had allopurinol prescription for kidney stones without identification of their nature and another 8 patients received the drug for recurrent calcium oxalate stones.

The limitations in our work could be due to the lack of analysis of the dose and duration of treatment for those patients who took the drug during the follow-up period. In addition, the specialty of physicians who prescribed allopurinol was not recorded that would help to improve the health care in general. Additionally, there was no chance to use ultrasound which could diagnose more cases of gouty arthritis in the presence of normal uric acid.

## Conclusion

Allopurinol is widely used all over the world for many indications. It is not free of adverse effects that could be fatal. Improper use of this medication had been documented in many centers including King Hamad University Hospital of Bahrain. Educational program and improved awareness of allopurinol among physicians are needed to eliminate over use of the drug and to avoid possible unnecessary life-threatening conditions.

## Abbreviations

KHUH: King Hamad University Hospital; ID: Identity number; CKD: Chronic kidney disease; HD: Hemodialysis; SJS: Steven Johnson syndrome; TEN: Toxic epidermal necrolysis; DRESS: Drug rash eosinophilia and systemic symptoms; DCS: Double contour sign

## Acknowledgements

The authors would like to acknowledge Alzaidi chair of research in rheumatic diseases, Faculty of Medicine, Umm Al Qura University, Makkah, Saudi Arabia, for supervising this work and conducting the statistical analysis. The authors would also like to thank Dr. Fatema Abdulmajeed Alhawaj, SHO internal medicine in KHUH, for assisting in writing

## Authors' contributions

SS: initiated the idea of the research, collected the related references, and wrote the manuscript. MM: shared in the analysis and interpretation of the patient's data and references' collection. All authors have read and approved the final version of the manuscript

## Funding

This study had no funding from any resource.

## Availability of data and materials

Available at KHUH Patients of rheumatology clinic and their electronic medical records on reasonable request.

## Ethics approval and consent to participate

Research and Ethics committee at King Hamad University Hospital has approved this study (Committee's reference number is Ref. KHUH/Research/ No. 221/2018 approved on 17 May 2018) and all patient were consented to participate verbally and ethics committee approved this procedure

## Consent for publication

Not applicable

## Competing interests

The authors declare that they have no competing interests.

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Received: 12 April 2020 Accepted: 18 May 2020

Published online: 15 September 2020

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