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Research Article

Allopurinol Prescription Patterns among Patients Attending Primary Health Care Centers in Qatar: A Retrospective Cross-Sectional Study

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Abstract

Introduction: Hyperuricemia is a medical condition associated with an increased incidence of comorbidities. Guidelines for the treatment of asymptomatic hyperuricemia remain controversial. Several studies have reported that allopurinol is overused worldwide. In Qatar, no national guidelines for hyperuricemia management or previous studies have evaluated allopurinol over prescription. The study aimed to determine the frequency of allopurinol overtreatment and investigate the associated factors. **Methods:** The retrospective cross-sectional study was conducted in Qatar on adult patients who were prescribed allopurinol for the first time at the Primary Health Care Corporation between 01 July 2021 and June 30, 2022. Data were extracted from patients' electronic medical records. Appropriate use of allopurinol was defined as for the presence of gout, kidney stones, or kidney disease, evidence of tophi, extremely high serum uric acid levels (>773.24 mmol/L in men or >594.8 mmol/L in women), or ongoing chemotherapy for malignancy in asymptomatic patients. **Results:** Our study included 1949 patients who received their first allopurinol prescription. The mean age was 45.66 years (standard deviation=10.57), with male predominance (75%). Only 17.39% were natives of Qatar, while the remaining were expatriates. The top three comorbidities were hypertension, dyslipidemia, and diabetes (44.38%, 42.74%, and 30.17%, respectively). Seventeen patients had no associated diagnosis with allopurinol prescriptions. Most patients had diagnoses related to hyperuricemia and gout (45.29% and 21.48%, respectively). Among 1932 patients, only 25.26% received an appropriate allopurinol prescription. The most commonly prescribed allopurinol dose was "100 mg daily" (89.38%). A statistically significant difference was discovered between appropriate and inappropriate allopurinol prescriptions in terms of sex ($p<0.001$). Diabetes, dyslipidemia, chronic kidney disease, and cerebrovascular disease were associated with an increased risk of inappropriate prescriptions, with p-values of 0.012, 0.025, <0.001, and 0.044, respectively. Normal and abnormal serum uric acid levels were significantly associated with an increased frequency of inappropriate prescriptions, whereas all patients with "extremely high" serum uric acid levels had valid allopurinol prescriptions ($p<0.001$). **Discussion:** Our study revealed that most allopurinol prescriptions in primary care facilities were not indicated. The implementation of clinical guidelines for the management of hyperuricemia is highly recommended.

Keywords: Allopurinol; Uric Acid; Gout; Hyperuricemia; Overtreatment; Inappropriate prescription

Introduction

Hyperuricemia is a medical condition associated with increased cardiovascular, renal, and metabolic comorbidities [1-3]. It is defined as a uric acid level ≥7 mg/dL (416 mmol/L) [3,4]. This condition is commonly encountered in clinical practice [5]. Hyperuricemia can be asymptomatic or result in uric acid deposition disorders, such as gout, tophi, and kidney stones [6,7]. In symptomatic patients, the treatment is indicated for gout, kidney stone formation, and nephropathy [8]. Guidelines for the treatment of asymptomatic hyperuricemia remain controversial [3,9]. The European Alliance of Associations for Rheumatology (EULAR), the British Society of Rheumatology, and the American College of Rheumatology do not recommend pharmacological treatment for patients with asymptomatic hyperuricemia [3]. According to existing evidence, the consensus is to treat asymptomatic hyperuricemia only in three conditions: first, when uric acid levels persistently exceed 13 mg/dL (773.24 mmol/L) in men and 10 mg/dL (594.8 mmol/L) in women, while these levels are set at lower limits in patients with gout, kidney stones, and hemodialysis [3,10]; second, when urinary uric acid excretion is beyond 1100 mg/day; and third, to prevent tumor lysis syndrome in cases of ongoing treatment for malignancy [10,11].

The treatment options for hyperuricemia include dietary modifications, weight loss, and pharmacological therapy with urate-lowering drugs [3]. The xanthine oxidase inhibitors allopurinol and febuxostat are the treatments of choice for hyperuricemia [12]. Allopurinol is the most prescribed medication for controlling uric acid levels [2,13]. However, many studies point to the overuse of this medication, and the inappropriate prescription of allopurinol is an identified issue all over the world [2,10,14,15]. According to previous studies, the prevalence of allopurinol overuse ranges from 46.9% in Thailand [15], 64% in Singapore [16], and 70.5% to 77.8% in the Kingdom of Saudi Arabia [10,11]. Few studies have been conducted in primary care settings or at the national level, and a small number have examined factors associated with inappropriate allopurinol prescription [17]. In these studies, patients without a confirmed diagnosis of gout or confirmed types of kidney stones were considered possible valid indications for allopurinol therapy, whereas insignificant hyperuricemia levels and undocumented diagnoses were considered invalid indications. Patients with malignancies, hemodialysis, chemotherapy, and hypersecretion of urinary uric acid (>1100 mg/day) were documented as valid candidates for allopurinol prescriptions [11,17].

Patients prescribed allopurinol inappropriately are unnecessarily exposed to the medication's potential side effects and adverse reactions without receiving any benefits from the drug regimen [16]. The side effects are usually mild, such as diarrhea, headache, and pruritic rash [8]. However, allopurinol can also trigger severe reactions, including hypersensitivity, a rare form of cutaneous adverse reaction that may cause significant morbidity and mortality [18]. Studies have established that the incidence of side effects is higher in patients with asymptomatic hyperuricemia as compared to other conditions [3]. It is important to select patients where therapeutic benefits outweigh the risks. Moreover, it is also essential to restrict allopurinol prescription when indicated.

In Qatar, a recent study published in 2022 revealed that the prevalence of asymptomatic hyperuricemia was 21.2% in young adults aged 40 and less with a clear association between prediabetes, dyslipidemia, and subclinical inflammatory markers [1]. However, there are no national guidelines for the treatment of hyperuricemia in Qatar. Furthermore, no previous studies have been conducted in Qatar to evaluate hyperuricemia treatment in general or primary care. There are no data on allopurinol overprescription in patients with hyperuricemia.

The study aims to explore the reasons and indications for allopurinol prescription in primary care and the detection of inappropriate prescriptions. The "Primary Health Care Corporation (PHCC)" is the public provider of primary care services in Qatar, operating and managing 31 health centers across the state in 2023.

Materials and Methods

Study Design

This is a descriptive cross-sectional retrospective study conducted among patients newly prescribed allopurinol in PHCC between July 1, 2021, and June 30, 2022. Only adult patients aged 18-65 years were included, and all patients with renewal/refill of the allopurinol prescription were excluded from the study.

Data Collection

Data were collected between December 2022 and March 2023 by the health information management team in PHCC from the electronic medical records program in the institution: "CERNER." Sociodemographic data, laboratory results, and clinical indications for allopurinol prescriptions were extracted from medical records. The data collection sheet included the following variables: age, sex, nationality, diagnosis, serum uric acid level within the past 12 months, comorbidities, Body Mass Index (BMI), allopurinol dose, and renal function (Glomerular Filtration Rate [GFR]).

We set the criteria for appropriate allopurinol use as the presence of gout, the presence of kidney stones or kidney disease, evidence of tophi, and in asymptomatic patients extremely high serum uric acid levels (>773.24 mmol/L in men or >594.8 mmol/L in women), or ongoing chemotherapy for malignancy. Patients who did not meet the criteria were considered to have invalid indications for allopurinol.

Ethical Considerations and Confidentiality

The study participants were not contacted, and identifiable information, such as names, healthcare numbers, phone numbers, addresses, or religions, was not collected. Age, sex, and nationality were encoded to ensure privacy. The data are in an encrypted file secured by a password stored on password-protected computers and only available to the research team.

The PHCC Department of Clinical Research and the Institutional Review Board (IRB) approved the study.

Statistical Analysis

Statistical analyses were performed using STATA 15.1 (College Station, TX, USA). The rate of appropriate allopurinol prescriptions was estimated. A chi-square test for goodness of fit was used to measure the association between the age groups, sex, nationality, BMI, comorbidities, and consolidated problems with appropriate and inappropriate prescriptions, expressed as frequencies in percentages. A p-value of < 0.05 was considered statistically significant with a 95% confidence interval.

Results

Our study included 1949 patients who were prescribed allopurinol for the first time during the study period. The mean age was 45.66 years (standard deviation=10.57), and the majority were men (n=1468; 75.32%) with most patients ranging between 41-50 years (n=609; 31.25%). Only 17.39% (n=339) were natives of Qatar and the remaining were expatriates. Regarding BMI, only 685 patients underwent weight and height measurements. Most of them were obese (n=413; 60.29%) and overweight (n=216; 31.53%) (Table 1).

	Number of Cases	Percentage (%)
Age Range (Years)		
18–20	17	0.87
21–30	124	6.36
31–40	517	26.53
41–50	609	31.25
51–60	499	25.60
60–65	183	9.39
Total	**1949**	**100**
Sex		
Men	1468	75.32
Women	481	24.68
Total	**1949**	**100**
Nationality		
Indian	363	18.62
Qatari	339	17.39
Egyptian	301	15.44
Filipino	259	13.29
Bangladeshi	94	4.82
Jordanian	78	4.00
Pakistani	77	3.95
Syrian	72	3.69
Sudanese	71	3.64
Others	295	15.14
Total	**1,949**	**100**
BMI Category		
Underweight	4	0.58
Normal	52	7.59
Overweight	216	31.53
Obese	413	60.29
Total*	**685**	**100**

*Missing 1264 patients due to lack of weight and height measurements at the first allopurinol prescription

Table 1: Demographic characteristics of all patients with first allopurinol prescription.

Hypertension (HTN) and dyslipidemia were the most common comorbidities (n=865; 44.38% and n=833; 42.74%, respectively), followed by diabetes (n=588; 30.17%). It should be noted that all patients had one or more comorbidities. Seventeen patients had no associated diagnosis for allopurinol prescription. Most patients had diagnoses related to hyperuricemia and gout (n=875; 45.29% and n=415; 21.48%, respectively). Sixty-four patients (3.31%) received an allopurinol prescription after a regular check-up visit to the physician (Table 2).

	Number of Cases	Percentage (%)
Comorbidities		
Hypertension	865	44.38
Dyslipidemia	833	42.74
Diabetes	588	30.17
Chronic Kidney Disease	136	6.98
Cardiovascular Disease	119	6.11
Cancer	40	2.05
Cerebrovascular Disease	29	1.49
Rheumatologic Disease	27	1.39
Liver Disease	15	0.77
Associated Diagnosis		
Hyperuricemia	875	45.29
Gout	415	21.48
Others/Non-Specific*	129	6.68
Musculoskeletal Problems**	78	4.04
Hypertension	74	3.83
Diabetes/Prediabetes	64	3.31
Regular Check-Up***	64	3.31
Chronic Kidney Disease	35	1.81
Kidney Stones	30	1.55
Lower Limb Problems (Non-Specific)****	28	1.45
Cardiovascular Problems	24	1.24
Knee Problems	21	1.09
Urinary Problems	21	1.09
Blood Disorders	20	1.03
Hyperuricuria	16	0.83
Infectious Problems	12	0.62
Thyroid Disorders	12	0.62
Lower Limb Problems (Specific)*****	6	0.31
Cancer	4	0.21
Liver Disease	4	0.21
Total	**1932**	**100**

*e.g., cough, colitis, watery eye, eczema; **e.g., arthralgia, back pain, shoulder pain; ***e.g., pre-employment screening, laboratory test requested, follow-up, well adult; ****e.g., burning feet, pain in the toe of the left foot, foot joint pain; *****e.g., calcaneal spur, plantar fasciitis, ankle sprain

Table 2: Comorbidities and associated diagnoses of all patients with the first allopurinol prescription.

According to the previously mentioned criteria, we identified that among the 1932 patients who had a diagnosis linked to allopurinol prescription only 488 (25.26%) had an appropriate prescription while a majority of patients were prescribed allopurinol inappropriately (n=1444; 74.74%) (Table 3). The seventeen patients without a diagnosis, when allopurinol was prescribed, were excluded from the analysis.

Prescription	Number of Cases	Percentage (%)
Appropriate	488	25.26
Inappropriate	1444	74.74
Total	**1932**	**100**

Table 3: Number of appropriate and inappropriate prescriptions of allopurinol.

In terms of uric acid levels, 1606 out of 1932 patients underwent serum uric acid measurements before the first allopurinol prescription. 429 patients had normal levels and 1104 had abnormal levels of serum uric acid. Normal or abnormal values were significantly associated with increased odds of having an inappropriate prescription of allopurinol instead of an appropriate one. Only 10 patients had "extremely high" serum uric acid levels, and all of them had valid allopurinol prescriptions ($p<0.001$) (Table 4).

Serum uric acid level	Appropriate	Inappropriate	Total	p-Value
Normal*	81 (16.6%)	411 (28.46%)	492 (25.47)	
Abnormal**	274 (56.15%)	830 (57.48%)	1104 (57.14%)	
Extremely Abnormal***	10 (2.05%)	0 (0%)	10 (0.52%)	
Missing****	123 (25.2%)	203 (14.06%)	326 (16.87%)	**< 0.001**
Total	**488 (100%)**	**1444 (100%)**	**1932 (100%)**	

*<416 mmol/L for both sexes; **416–773.24 mmol/L in men or 416–594.8 mmol/L in women; ***> 773.24 mmol/L in men or >594.8 mmol/L in women; ****Missing 326 patients did not have serum uric acid levels done before their first allopurinol prescription

Table 4: Number of appropriate and inappropriate prescriptions of allopurinol according to serum uric acid levels.

As for the most allopurinol dose, we discovered that in the majority of cases with a percentage reaching 89.38% "100 mg daily" was prescribed, followed by the prescription of "300 mg daily" dose (6.99%). Our data also revealed that among the 35 patients who received allopurinol for an associated diagnosis of chronic kidney disease, the majority (n=24; 92.31%) received the "100 mg daily" allopurinol dose for hyperuricemia management.

In terms of demographic variables, our results demonstrated a statistically significant difference between appropriate and inappropriate prescriptions of allopurinol in terms of sex ($p<0.001$) (Table 5).

	Appropriate	Inappropriate	Total	p-Value
Age Range (Years)				
18–20	3 (1%)	14 (1%)	17	
21–30	25 (5%)	99 (7%)	124	
31–40	148 (30%)	365 (25%)	513	
41–50	143 (29%)	461 (32%)	604	0.167
51–60	118 (24%)	375 (26%)	493	
60–65	51 (11%)	130 (9%)	181	
Gender				

Male	414 (85%)	1040 (72%)	1454	**< 0.001**
Female	74 (15%)	404 (28%)	478	
Nationality				
Indian	90 (18.44%)	271 (18.77%)	361	0.079
Qatari	85 (17.42%)	252 (17.45%)	337	
Egyptian	64 (13.11%)	237 (16.41%)	298	
Filipino	68 (13.93%)	191 (1.23%)	259	
Bangladeshi	29 (5.94%)	65 (4.50%)	94	
Jordanian	22 (4.51%)	55 (3.81%)	77	
Pakistani	10 (2.05%)	66 (4.57%)	76	
Syrian	16 (3.28%)	54 (3.74%)	70	
Sudanese	16 (3.28%)	54 (3.74%)	70	
Others	88 (18.03%)	199 (13.78%)	287	
BMI*				
Underweight	2 (1.27%)	2 (0.39%)	4	0.533
Normal	10 (6.37%)	42 (8.11%)	52	
Overweight	48 (30.57%)	164 (31.66%)	212	
Obese	97 (61.78%)	310 (59.85%)	407	
* For BMI, the total number of appropriate and inappropriate dispenses was 157 and 518, respectively.				

Table 5: Appropriateness and inappropriateness of allopurinol prescribing in correlation with demographic characteristics.

In addition, the existence of certain comorbidities exhibited statistical significance in their relationship with the appropriateness of allopurinol prescriptions. The presence of each of diabetes, dyslipidemia, chronic kidney disease, and cerebrovascular disease was significantly associated with an increased frequency of inappropriate prescriptions when compared to their absence, with p-values of 0.012, 0.025, <0.001, and 0.044, respectively (Table 6). While the other comorbidities did not demonstrate a statistically significant association with the pattern of allopurinol prescription, we discovered a higher number of inappropriate than appropriate allopurinol prescriptions.

Comorbidities	**Appropriate (n=488)**	**Inappropriate (n=1444)**	**Total**	**p-Value**
Hypertension	206 (42%)	655 (45%)	861	0.227
Dyslipidemia	185 (38%)	631 (44%)	816	**0.025**
Diabetes	126 (26%)	460 (32%)	586	**0.012**
Chronic Kidney Disease	62 (13%)	72 (5%)	134	**<0.001**
Cardiovascular Disease	35 (7%)	83 (6%)	118	0.256
Cancer	14 (3%)	25 (2%)	39	0.122
Cerebrovascular Disease	12 (3%)	17 (1%)	29	**0.044**

Rheumatologic Disease	10 (2%)	17 (1%)	27	0.156
Liver Disease	5 (1%)	10 (1%)	15	0.470

Table 6: Association for comorbidities with allopurinol prescription appropriateness.

Discussion

Our study demonstrated that most allopurinol prescriptions were inappropriate, thus exposing patients to unnecessary medications and their potential adverse effects. The finding is similar to those of several previous studies conducted in other countries. It also confirms that this is a problem encountered not only in primary care but also in secondary and tertiary care, as revealed in studies from the Kingdom of Saudi Arabia and Thailand, which were all conducted in tertiary care centers and teaching hospitals, respectively [10,11,15]. Our result is close to the percentage of non-valid prescriptions from two studies conducted in the Kingdom of Saudi Arabia, ranging from 70.5% to 77.8% [10,11], but higher than in Thailand and Singapore (46.9% and 64%, respectively) [15,16]. Allopurinol overprescription is a global problem not limited to our region. Several factors can explain the higher number of inappropriate prescriptions in the Gulf region. First, physicians might be pressured by patients to prescribe medications for hyperuricemia as patients might consider a high uric acid level to be harmful. Second, hyperuricemia can progress to gout which induces an inflammatory process and increases cardiovascular risk [19]. Physicians may think that treating hyperuricemia will prevent gout and its complications thus decreasing cardiovascular risk. This could explain why comorbidities, such as

Dyslipidemia, diabetes, chronic kidney disease, and cerebrovascular disease, were associated with an increased risk of inappropriate prescriptions in our study.

Hyperuricemia was the most common clinical indication for which allopurinol was prescribed. Asymptomatic hyperuricemia should not be treated pharmacologically. However, physicians may consider an elevated uric acid level an abnormality. They may feel erroneously forced to treat it by prescribing medication, even if not clinically indicated. Another interesting finding in our study was that 326 patients did not have serum uric acid levels measured before allopurinol was prescribed; therefore, we could not determine whether there was a high uric acid level.

Physicians are responsible for providing the best medicine to patients, as they must consider the benefits and risks of each intervention [10]. Halting inappropriate allopurinol prescriptions is the responsibility of doctors who must share their awareness with both patients and colleagues [10]. Further studies should investigate the rationale behind physician prescriptions of allopurinol. Following the study, providing doctors with clear guidelines for uric acid management can optimize allopurinol prescription and limit its preventable potential side effects. A similar study can be conducted to evaluate this report's impact on medical practice at PHCC and monitor the allopurinol prescription pattern.

The strengths of our study include the substantial number of patients from different regions throughout the country and the fact that it was not limited to a city or health center. Compared to a similar study conducted in the Kingdom of Saudi Arabia, the number of patients was approximately the same, but this number was collected only from one hospital compared to our study, where patients were collected from more than 30 different health centers from various locations. In addition, our study was one of the few to determine the relationship between some comorbidities and allopurinol prescription patterns [11,17], as it was discovered that patients with certain diagnoses were significantly more likely to receive allopurinol for uric acid management.

However, the study had a few limitations. Prescription of other urate-lowering drugs was not included because other medications were not available at the PHCC. Several studies have demonstrated that allopurinol is the most commonly prescribed urate-lowering drug [2,13]. On the other hand, the appropriateness of the use of allopurinol was evaluated based on the clinical diagnosis chosen by the treating physician and linked to the medication prescription. Some of the diagnoses were misleading and nonspecific for example: "pain of toe of left foot, arthritis, arthralgia..." or non-clinical for example: "drug prescription, laboratory test result, telemedicine consultation done with patient." In our study, such diagnoses were included in the inappropriate category, but they carried the possibility of appropriate prescriptions according to the patient's symptom history or laboratory findings. This may have underestimated the appropriateness of allopurinol in this study. However, a sensitivity analysis was done after assuming that these diagnoses were related to an appropriate prescription; the results kept the frequency of the inappropriate ones much higher. Also, an examination of the possible side effects related to allopurinol overtreatment would be a good addition and should have been investigated in another report.

Conclusion

Our study revealed that most allopurinol prescriptions in primary care units were not indicated. Implementing clinical guidelines regarding the management of hyperuricemia, particularly in PHCC or more broadly in Qatar, is highly recommended to improve the management of hyperuricemia and gout.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Conception and Design

AI and HC; acquisition, analysis, and interpretation of data: JK, AI, and HC; drafting of the article: HC and AI; critical revision for important intellectual content: SA and JK; approval of the final

version of the manuscript: HC, AI, JK, and SA.

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