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Racial Disparities in the Risk of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis as Urate-Lowering Drug Adverse Events in the US

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Abstract

Objectives—*HLA-B*5801* allele carriage (a strong determinant of allopurinol hypersensitivity syndrome) varies substantially among races, which may lead to racial disparities in the risk of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) in the context of urate-lowering drug adverse events (ULDAEs). We examined this hypothesis in a large, racially diverse, and generalizable setting.

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Methods—Using a database representative of US hospitalizations (2009-2013), we investigated the racial distribution of hospitalized SJS/TEN (principal discharge diagnosis) as ULDAEs (ICD-9-CM Classification of External Causes). Our reference groups included the US Census population, US allopurinol users, and ULDAE hospitalizations without SJS/TEN.

Results—We identified 606 cases hospitalized for SJS/TEN as ULDAEs (mean age, 68 years; 44% male), among which there was an overrepresentation of Asians (27%) and Blacks (26%), and an underrepresentation of Whites (29%) and Hispanics (% too-low-to-report), compared with the US Census population (5%, 12%, 67%, and 15%, respectively). The hospitalization rate ratios for SJS/TEN among Asians, Blacks, and Whites were 11.9, 5.0, and 1.0 (referent), respectively. These associations persisted using other national referents. According to the NHANES 2009-2012, allopurinol constituted 96.8% of urate-lowering drug use, followed by probenecid (2.1%).

Conclusions—These national data indicate that Asians and Blacks have a substantially higher risk of SJS/TEN as ULDAEs than Whites (or Hispanics), correlating well with corresponding frequencies of *HLA-B*5801* in the US population (i.e., 7.4%, 4%, 1%, and 1%, respectively). Given its market dominance and established association with SJS/TEN, our findings support the use of vigilance in these minorities when considering allopurinol.

Keywords

Race; Allopurinol; Urate-Lowering Therapy; Stevens-Johnson Syndrome; Toxic Epidermal Necrolysis; Gout

INTRODUCTION

Allopurinol (a xanthine oxidase inhibitor) is the most commonly used, first-line urate-lowering drug (ULD) constituting >96% of ULD use in the US (1,2). Although uncommon, the most feared adverse event of ULD is severe allopurinol hypersensitivity syndrome (AHS), primarily manifesting as severe cutaneous reactions (i.e., Stevens-Johnson Syndrome [SJS] and Toxic Epidermal Necrolysis [TEN]). To that effect, other oral ULDs such as probenecid or febuxostat are recommended as the first alternative therapy in patients with AHS (2-5). For example, the Taiwanese Food and Drug Administration has recently adopted a policy to use febuxostat as an alternative first-line ULD for patients with chronic kidney disease (CKD) to avoid severe AHS (3).

SJS/TEN due to AHS frequently involves major organs and can be fatal in up to 32% of cases, and survivors are often left with substantial sequelae of involved organs (e.g., corneal damage and renal insufficiency) (3). A wide range of risk estimates for AHS have been reported (e.g., 0.4% to 0.07%) (3,6), and a previous study found allopurinol to be the most common cause of both SJS and TEN in Europe and Israel (7).

As such, there are major unmet needs to improve risk management and provider and public perception of allopurinol safety, which would in turn help to improve the widely-recognized suboptimal control of gout in current medical practice (8-14). Furthermore, as allopurinol is increasingly being used and evaluated for its potential therapeutic impact on cardiovascular-renal conditions even among those without gout (3,15), an accurate understanding of the risk factors for these serious adverse events is even more critical.

Beyond the increased risk of AHS among CKD patients (16,17), recent pharmacogenetic studies have found that the *HLA-B*5801* allele is strongly associated with an increased risk of AHS in certain Asian populations (Korean, Han Chinese, Japanese, and Thai populations) (18-22), as well as in a European population (23). While individual AHS odds ratios (ORs) were as high as 580 in Han Chinese (24), a meta-analysis of published studies found an 80 to 97 times increased risk of developing AHS among allopurinol users with the *HLA-B*5801* allele compared to those without the allele (25). These data helped inform the 2012 American College of Rheumatology (ACR) guidelines for gout management (4), which recommended screening for this marker among selected Asian populations whose frequency of *HLA-B*5801* carriage is high.

Han Chinese have a frequency of *HLA-B*5801* carriage as high as over 20% (26). In contrast, the other races were found to carry lower, yet varying frequencies of *HLA-B*5801* (i.e., 4%, 1%, and 1%, among Blacks, Whites, and Hispanics in the US population, respectively) (26). These varying frequencies of *HLA-B*5801* across different races could lead to major racial disparities in the risk of SJS/TEN in the context of urate-lowering drug adverse events (ULDAEs). Such information on racial and ethnic descent (even before considering genotyping) could immediately contribute to risk stratification to prevent these severe adverse events in gout care.

To test this hypothesis in a large, racially diverse, and generalizable context, we examined potential racial disparities in the risk of SJS/TEN in the context of ULDAEs using a US nationwide inpatient dataset from 2009-2013.

METHODS

Data Sources

The Nationwide Inpatient Sample (NIS), developed by the Agency for Healthcare Research and Quality (AHRQ), is a nationally representative, all-payer inpatient care database in the US (27). It represents between 5 and 8 million discharges per year (a 20% stratified sample of all non-federal, non-rehabilitation hospitals in the country). Each hospitalization is anonymized and recorded in the NIS as a unique entry with one principal discharge diagnosis and up to 24 secondary diagnoses. Demographic information (race, age, and sex) are recorded for each hospitalization. Data quality assessments of the NIS are conducted annually, thereby guaranteeing the internal validity of the database (28). Furthermore, comparisons against the following data sources are made to strengthen the external validity of the NIS: the American Hospital Association Annual Survey Database, the National Hospital Discharge Survey from the National Center for Health Statistics, and the MedPAR inpatient data from the Centers for Medicare and Medicaid Services (28).

Study Design

We examined the racial distribution among hospitalizations in the US from 2009-2013 with a principal discharge diagnosis of SJS/TEN (ICD-9-CM 695.13-15), in combination with a secondary discharge diagnosis of an adverse effect caused by uric acid metabolism drugs in therapeutic use (ICD-9-CM Classification of External Causes E9447, representing

hospitalizations for ULDAEs). These hospitalizations for SJS/TEN as physician-determined ULDAEs are expected to be almost exclusively (if not all) due to allopurinol, given its established association with SJS/TEN (2,3) and its market dominance in the US. For example, according to our analysis of the National Health and Nutrition Examination Survey (NHANES) 2009-2012 (the latest available data), allopurinol constituted 96.8% of ULD use, followed by probenecid (2.1%), which is not known to cause SJS/TEN.

We examined the following reference data for our racial distribution comparison: (1) the US Census population, (2) US allopurinol users (from the NHANES), and (3) those with a secondary discharge diagnosis of ULDAEs, but without a principal diagnosis of SJS/TEN identified in the NIS. Further, we also presented the racial distribution of US gout patients (from the NHANES) as well as that of all gout hospitalizations (from the NIS) as additional referents.

Statistical Analyses

All analyses were performed using hospital-level sampling weights provided by the NIS to obtain US national estimates. As the NIS can potentially include recurrent admissions with SJS/TEN as ULDAEs, we identified and excluded potential repeated admissions by the same subjects, which were found to be <1% of all such admissions, using a published algorithm (based on age, sex, race, income, health insurance, hospital identification code, and year of admission) (29). Thus, our analysis included only unique individuals for SJS/TEN as ULDAEs (i.e., >99% of all admissions).

We first calculated race-specific hospitalization rates with SJS/TEN as ULDAEs per 1,000,000 US adults (using US Census data), and their rate ratios with Whites as the referent. We repeated the same analyses using US allopurinol users as the denominator based on the NHANES 2011-2012. We used these overlapping calendar years of the NHANES specifically due to the availability of Asian race data, unlike other NHANES years. The NHANES collected data on medication use in the prior 30-day period, including ULDs (30). These NHANES analyses were performed adjusting for clusters and strata of the complex sample design and to incorporate sample weights (31).

Further, for a comparison analysis within the NIS, we compared the racial distributions between ULDAE cases with and without SJS/TEN as the principal discharge diagnosis. For these analyses, we calculated ORs for the association between race and SJS/TEN using logistic regression, adjusting for age and sex. Race is determined at birth; thus, factors that occur after birth (e.g., CKD) cannot confound race effects on AHS. We tested this by adjusting for potentially relevant covariates (including CKD) in our NIS analyses. Regardless, according to our NHANES analysis, the mean GFR values in gout patients or allopurinol users among Whites, Blacks, and Asians were 75.1, 77.3, and 76.2 mL/min/1.73m², respectively, and the corresponding proportions of CKD stage 2 were 66.3%, 51.0%, and 57.4%. Finally, we calculated in-hospital mortality, length of stay, and hospitalization charges according to race.

In compliance with the Healthcare Cost and Utilization Project Data Use Agreement (32), we did not report data when the tabulated cell size was 10 or fewer. All p-values were 2-

sided with a significance threshold of $p < 0.05$. Statistical analyses were performed using SAS Version 9.3 (SAS Institute, Cary, North Carolina).

RESULTS

During 2009-2013 in the US, there were 606 patients hospitalized for SJS/TEN as ULDAEs (mean age, 68 years; 44% male) (Table 1). Of these 606, 57 (9%) died during hospitalization, the average length of stay was 14 days (10 days for SJS and 20 days for TEN), and the average charge per hospitalization was \$157,334 USD (\$60,318 for SJS and \$324,259 for TEN).

Race Distribution of Hospitalized SJS/TEN as ULDAEs in the US Population

Of the SJS/TEN patients with ULDAEs ($n=606$), there was a substantial over-representation of Asians (27%) and Blacks (26%) as compared to Whites (29%), compared with the US population race distribution (5%, 12%, and 67%, respectively) (Table 2 and Figure 1). The corresponding hospitalization rate ratios for SJS/TEN were 11.9, 5.0, and 1.0 (referent), among Asians, Blacks, and Whites, respectively (Table 2). Although Hispanics were the largest minority race according to the US Census data (i.e., 15%) during the study period, the number of SJS/TEN cases as ULDAEs was too small to report (i.e., unweighted $N < 10$) (32), suggesting that the frequency of SJS/TEN cases among Hispanics is unlikely to be higher than any other race.

Race Distribution Comparison with US Allopurinol Users from the NHANES

The racial proportions of US allopurinol users according to the NHANES 2011-2012 were 2%, 13%, 2%, and 81% among Asians, Blacks, Hispanics, and Whites, respectively (Figure 2). This was consistent with the proportion of Blacks in the US population, whereas Asians and Hispanics were both underrepresented. The corresponding hospitalization rate ratios for SJS/TEN as ULDAEs among allopurinol users were 32.6, 5.7, and 1.0 (referent) for Asians, Blacks, and Whites, respectively (Table 2). These estimates tended to be larger than those compared to the US Census data above, as the rate of allopurinol use in the US population tended to be lower among minority patients as compared to Whites (Figure 2). Given the small number of SJS/TEN cases as ULDAEs among Hispanics in the NIS, (32) their estimate was not reported. In addition, the racial proportions of US gout patients were similar to those of US allopurinol users, except for Asians, which were reflective of the US population (Figure 2).

Race Distribution Comparison between Hospitalizations for ULDAEs with and without SJS/TEN in the NIS

The race proportions of the internal comparison groups from the NIS (i.e., ULDAE admissions without SJS/TEN as the principal discharge diagnosis [6%, 18%, and 60% among Asians, Blacks, and Whites, respectively]) tended to reflect the race distributions of the US (Figure 3). The corresponding ORs for SJS/TEN among ULDAE cases were 8.3, 2.9, and 1.0 (referent), respectively (Table 2). Adjusting for age and sex did not change these ORs materially (Table 2). Similarly, adjusting for relevant comorbidities including CKD (derived from secondary discharge diagnoses) did not change the ORs materially (Table 2).

Given the small number of SJS/TEN cases as ULDAEs among Hispanics (32), their estimate was not reported. In addition, the racial proportions of non-SJS/TEN cases were similar to the overall hospitalized cases of gout in the NIS (Figure 3).

DISCUSSION

Our findings based on data representative of the US (an ethnically and racially diverse nation) indicate that race is a strong predictor for the risk of SJS/TEN as ULDAEs. The risk of SJS/TEN among Asians and Blacks was 12 and 5 times higher than among Whites, respectively. These strong associations persisted using several comparison reference groups. In contrast, the frequency of these serious events was low among Hispanics despite their being the largest minority group in the US during the study period, suggesting that their risk is unlikely to be larger than Whites or other races. As hypothesized, these race-associated varying risk levels correlate well with their corresponding frequencies of *HLA-B*5801* in the US population (i.e., 7.4%, 4%, 1%, and 1% among Asians, Blacks, Whites, and Hispanics, respectively) (26). As allopurinol is the only ULD with an established association with SJS/TEN—and in light of its market dominance in the US—our findings support the use of extra caution among Asians and Blacks when considering allopurinol, and support the ACR recommendation to screen for *HLA-B*5801* for high-risk Asians (4).

We found that the risk of SJS/TEN as ULDAEs is approximately 12 times higher among Asians than Whites in the US. A recent Taiwanese population-based study (3) also reported an incidence rate of hospitalized AHS that is higher than that from a US study of Medicaid data from five states (6) (2 vs 0.69 cases per 1000 incident allopurinol users, respectively). Furthermore, the latter US study found the proportion of Whites among AHS cases to be considerably underrepresented (i.e., 24%) (6), similar to our results, although that study did not report data on any minority races. Moreover, a New Zealand study found an increased risk of AHS among Chinese descendants compared with European descendants (OR = 24.2 [95% CI, 3.0 to 199.0]) (16). These data collectively indicate that there is a substantially higher risk of allopurinol-induced SJS/TEN among Asians compared to Whites, reflecting their respective allele frequencies of *HLA-B*5801* (26). To that effect, the Taiwanese Food and Drug Administration has recently adopted a new ULD prescription policy to use febuxostat as an alternative first-line ULD for CKD patients to help reduce allopurinol-associated SJS/TEN, given the race-associated high background risk in their population (3).

As in many other national data, the NIS combines many diverse US Asian populations (e.g., Chinese, Asian Indians, Filipinos, Vietnamese, Koreans, and Japanese) together into one category. Thus, our results should be interpreted as the average effect of these diverse Asian groups, similar to the allele frequency estimates of *HLA-B*5801* among US Asians (i.e., 7.4%) (26). To that effect, it should be noted that the US Japanese population has a low allele frequency of *HLA-B*5801* (0.8%), which is similar to US Whites as well as the Japanese population of Japan (0.6%) (26). Thus, although the NIS did not allow for risk estimation specifically among US Japanese individuals, we expect a risk level similar to that of Whites, which appears to be anecdotally the case in Japan (through personal communications) where ULD is used to treat asymptomatic hyperuricemia, particularly when combined with cardiovascular-renal-metabolic comorbidities (33). In contrast, a recent

Taiwanese study warns against such practice (3) (similar to many other countries' recommended practice) (34) based on their finding that asymptomatic hyperuricemia associated with renal or cardiovascular diseases predicts an increased risk of AHS (3).

To our knowledge, the present study provides the first evidence that US Blacks have a higher risk of SJS/TEN as ULDAEs than US Whites. These findings were also reflective of their allele frequencies of *HLA-B*5801* (e.g., 4% vs. 1% in the US, respectively). In other countries, the allele frequencies among Blacks are even higher (e.g., 7 to 10% in Kenya and 8% in South Africa) (26) and thus, one would expect that their risk of AHS would be higher than what we have observed in the US. Given these collective findings, the recommendation to screen for *HLA-B*5801* or the use of alternative ULD (3) may also apply to Blacks who are candidates for allopurinol, particularly when there are co-existing risk factors such as CKD (16,17). Although Hispanics were the largest minority race group in the US during the study period (i.e., 14%), there was an insufficient number of cases of SJS/TEN as ULDAEs to allow reporting in compliance with the Healthcare Cost and Utilization Project Data Use Agreement (32). Apart from the likely lower risk of AHS in Hispanics, our findings may also be explained by the generally lower rate of access to gout care among this minority population (as supported by our NHANES findings), which may be worse than for other racial minority group. Nevertheless, our data were consistent with the low frequency of *HLA-B*5801* reported among Hispanics in the US and among Mexicans (i.e., ~1%) (26).

Several strengths of our study deserve comment. The NIS database is an all-payer inpatient database in the US representative of hospitalizations of the general population. Therefore, both the large scale and the ethnic diversity of the US general population made it possible to directly compare these rare but serious AEs among different racial minority groups, which would not be feasible in ethnically homogenous countries, regardless of their size. Further, our findings provide "real world" data with a high level of generalizability. Our study also employed multiple reference groups from several external and internal national data sources (i.e., the US Census, NHANES, and NIS) in a complementary manner, adding to the robustness of our findings.

There are also potential limitations to our study. Because the NIS database is an administrative database, certain levels of misclassification of diagnostic codes may be inevitable. However, the specific and distinctive nature of the primary end-points (i.e., SJS/TEN), in-hospital mortality, and length of hospital stay strongly corroborate their validity. The NIS lacks medication data, and thus we were not able to examine the direct contributions of allopurinol to the observed associations. Nevertheless, given allopurinol's extreme market dominance during the study period (>96% of ULD use and approximately 99% of xanthine oxidase inhibitors), the SJS/TEN hospitalizations as ULDAEs observed in the current study are expected to be almost exclusively (if not all) due to allopurinol use. Furthermore, as noted earlier, other ULDs are considered safe alternatives in patients with AHS (2-5). Thus, it is extremely unlikely that the small proportion of other ULDs available in the US (i.e., probenecid, febuxostat, and pegloticase) would have contributed to SJS/TEN in the context of ULDAEs, and that this risk would have varied in such a substantial manner as observed according to race. Finally, as stated earlier, race cannot be confounded by CKD or other covariates that occur after birth, which is supported by our comorbidity-adjusted

results of the NIS. Nevertheless, it would be valuable to examine the potential impact of other known risk factors at the time of ULD initiation, as well as the potential role of dose escalation, compliance, and duration of use according to race in future studies.

In conclusion, our findings based on these nationally representative inpatient data indicate that Asians and Blacks have a substantially higher risk of SJS/TEN as ULDAEs than Whites (or Hispanics), correlating well with corresponding frequencies of HLA-B*5801 in the US population. Together with its market dominance and well-established association with SJS/TEN, these findings support the use of vigilance in these minorities when considering allopurinol.

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REFERENCES

1. Jutkowitz E, Choi HK, Pizzi LT, Kuntz KM. Cost-effectiveness of allopurinol and febuxostat for the management of gout. *Ann Intern Med.* 2014; 161:617–26. [PubMed: 25364883]
2. Stern RJ. Reducing Life-Threatening Allopurinol Hypersensitivity. *JAMA internal medicine.* 2015; 175:1558. [PubMed: 26192474]
3. Yang CY, Chen CH, Deng ST, Huang CS, Lin YJ, Chen YJ, et al. Allopurinol Use and Risk of Fatal Hypersensitivity Reactions: A Nationwide Population-Based Study in Taiwan. *JAMA internal medicine.* 2015; 175:1550–7. [PubMed: 26193384]
4. Khanna D, Fitzgerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. American College of Rheumatology guidelines for management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. *Arthritis care & research.* 2012; 64:1431–46. 2012. [PubMed: 23024028]
5. Saokaew S, Tassaneeyakul W, Maenthaisong R, Chaiyakunapruk N. Cost-effectiveness analysis of HLA-B*5801 testing in preventing allopurinol-induced SJS/TEN in Thai population. *PLoS One.* 2014; 9:e94294. [PubMed: 24732692]
6. Kim SC, Newcomb C, Margolis D, Roy J, Hennessy S. Severe cutaneous reactions requiring hospitalization in allopurinol initiators: a population-based cohort study. *Arthritis care & research.* 2013; 65:578–84. [PubMed: 22899369]
7. Halevy S, Ghislain PD, Mockenhaupt M, Fagot JP, Bouwes Bavinck JN, Sidoroff A, et al. Allopurinol is the most common cause of Stevens-Johnson syndrome and toxic epidermal necrolysis in Europe and Israel. *J. Am. Acad. Dermatol.* 2008; 58:25–32. [PubMed: 17919772]
8. Neogi T. Clinical practice. Gout. *N Engl J Med.* 2011; 364:443–52. [PubMed: 21288096]
9. Rees F, Hui M, Doherty M. Optimizing current treatment of gout. *Nature reviews. Rheumatology.* 2014; 10:271–83. [PubMed: 24614592]
10. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. *Ann Rheum Dis.* 2015; 74:661–7. [PubMed: 24431399]
11. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Eligibility for and prescription of urate-lowering treatment in patients with incident gout in England. *JAMA.* 2014; 312:2684–6. [PubMed: 25536262]
12. Edwards NL. Quality of care in patients with gout: why is management suboptimal and what can be done about it? *Curr Rheumatol Rep.* 2011; 13:154–9. [PubMed: 21161617]
13. Doherty M. New insights into the epidemiology of gout. *Rheumatology (Oxford).* 2009; 48(Suppl 2):ii2–ii8. [PubMed: 19447779]

14. Dalbeth N, Stamp LK. Gout: Why compare the effectiveness of suboptimal gout management? *Nature reviews. Rheumatology*. 2015
15. <https://clinicaltrials.gov/>
16. 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 Rheum*. 2012
17. Hande KR, Noone RM, Stone WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med*. 1984; 76:47–56. [PubMed: 6691361]
18. Kang HR, Jee YK, Kim YS, Lee CH, Jung JW, Kim SH, et al. Positive and negative associations of HLA class I alleles with allopurinol-induced SCARs in Koreans. *Pharmacogenetics and genomics*. 2011; 21:303–7. [PubMed: 21301380]
19. Jung JW, Song WJ, Kim YS, Joo KW, Lee KW, Kim SH, et al. HLA-B58 can help the clinical decision on starting allopurinol in patients with chronic renal insufficiency. *Nephrol. Dial. Transplant*. 2011; 26:3567–72. [PubMed: 21393610]
20. Hung SI, Chung WH, Liou LB, Chu CC, Lin M, Huang HP, et al. HLA-B*5801 allele as a genetic marker for severe cutaneous adverse reactions caused by allopurinol. *Proc. Natl. Acad. Sci. U. S. A*. 2005; 102:4134–9. [PubMed: 15743917]
21. Kaniwa N, Saito Y, Aihara M, Matsunaga K, Tohkin M, Kurose K, et al. HLA-B locus in Japanese patients with anti-epileptics and allopurinol-related Stevens-Johnson syndrome and toxic epidermal necrolysis. *Pharmacogenomics*. 2008; 9:1617–22. [PubMed: 19018717]
22. Tassaneeyakul W, Jantararoungtong T, Chen P, Lin PY, Tiamkao S, Khunarkornsiri U, et al. Strong association between HLA-B*5801 and allopurinol-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in a Thai population. *Pharmacogenetics and genomics*. 2009; 19:704–9. [PubMed: 19696695]
23. Lonjou C, Borot N, Sekula P, Ledger N, Thomas L, Halevy S, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. *Pharmacogenetics and genomics*. 2008; 18:99–107. [PubMed: 18192896]
24. Zineh I, Mummaneni P, Lyndly J, Amur S, La Grenade LA, Chang SH, et al. Allopurinol pharmacogenetics: assessment of potential clinical usefulness. *Pharmacogenomics*. 2011; 12:1741–9. [PubMed: 22118056]
25. Somkrur R, Eickman EE, Saokaew S, Lohitnavy M, Chaiyakunapruk N. Association of HLA-B*5801 allele and allopurinol-induced Stevens Johnson syndrome and toxic epidermal necrolysis: a systematic review and meta-analysis. *BMC medical genetics*. 2011; 12:118. [PubMed: 21906289]
26. [<http://www.allelefrequencies.net/>]
27. Prior IA, Welby TJ, Ostbye T, Salmond CE, Stokes YM. Migration and gout: the Tokelau Island migrant study. *British Medical Journal Clinical Research Ed*. 1987; 295:457–61. [PubMed: 3117170]
28. Patel NJ, Deshmukh A, Pant S, Singh V, Patel N, Arora S, et al. Contemporary trends of hospitalization for atrial fibrillation in the United States, 2000 through 2010: implications for healthcare planning. *Circulation*. 2014; 129:2371–9. [PubMed: 24842943]
29. Chung L, Krishnan E, Chakravarty EF. Hospitalizations and mortality in systemic sclerosis: results from the Nationwide Inpatient Sample. *Rheumatology (Oxford)*. 2007; 46:1808–13. [PubMed: 17986481]
30. Juraschek SP, Kovell LC, Miller ER 3rd, Gelber AC. Gout, urate-lowering therapy, and uric acid levels among adults in the United States. *Arthritis care & research*. 2015; 67:588–92. [PubMed: 25201123]
31. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population. *Arthritis Rheum*. 2011; 63:3136–41. [PubMed: 21800283]
32. <https://www.hcup-us.ahrq.gov/team/NationwideDUA.jsp>
33. Yamanaka H, Metabolism TG. Essence of the revised guideline for the management of hyperuricemia and gout. *Japan Medical Association journal: JMAJ*. 2012; 55:324–9. [PubMed: 25237241]

34. Richette P, Perez-Ruiz F, Doherty M, Jansen TL, Nuki G, Pascual E, et al. Improving cardiovascular and renal outcomes in gout: what should we target? *Nature reviews. Rheumatology*. 2014; 10:654–61. [PubMed: 25136785]

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Figure 1. Race Distribution of SJS/TEN Hospitalizations for ULDAE Compared with the US Population

SJS/TEN = Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis; ULDAE = Urate-Lowering Drug Adverse Event

*These groups are combined as the unweighted cell size of each was 10 or fewer, in which case individual group reporting is not allowed according to the Healthcare Cost and Utilization Project Data Use Agreement.

Figure 2. Race Distribution of SJS/TEN Hospitalizations for ULDAE Compared with US Gout Patients or Allopurinol Users

SJS/TEN = Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis; ULDAE = Urate-Lowering Drug Adverse Event

*These groups are combined as the unweighted cell size of each was 10 or fewer, in which case individual group reporting is not allowed according to the Healthcare Cost and Utilization Project Data Use Agreement.

Figure 3. Race Distribution according to SJS/TEN Hospitalizations for ULDAE in the NIS
 SJS/TEN = Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis; ULDAE = Urate-Lowering Drug Adverse Event

*These groups are combined as the unweighted cell size of each was 10 or fewer, in which case individual group reporting is not allowed according to the Healthcare Cost and Utilization Project Data Use Agreement.

Table 1
Demographics of Patients with SJS/TEN as ULDAE (N=606)

Age (years), Mean $\pm$ SE	68 + 1
Male, N (%)	266 (44)
Race, N (%)	
White	175 (29)
Black	155 (26)
Asian	163 (27)
Hispanics, Other Races, and Missing [*]	114 (18)

SJS/TEN = Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis; ULDAE = Urate-Lowering Drug Adverse Event

^{*} These groups are combined as the unweighted cell size of each was 10 or fewer, in which case individual group reporting is not allowed according to the Healthcare Cost and Utilization Project Data Use Agreement. Missing was less than 7% of the total.

Table 2
SJS/TEN Hospitalizations with ULDAE (N=606)*

Race	White	Black	Asian
Among US Adults According to Race			
Hospitalizations, N	175	155	163
Hospitalizations per 1,000,000 US adults	0.22	1.10	2.64
Hospitalization rate ratio (95% CI)	1.0 (ref)	5.0 (4.0 to 6.2)	11.9 (9.6 to 14.8)
Among US Allopurinol Users According to Race			
US adults with allopurinol use, N	1,840,829	283,564	52,536
Hospitalizations, N	175	155	163
Hospitalizations per 1,000,000 with allopurinol users	19.0	109.3	620.5
Hospitalization rate ratio (95% CI)	1.0 (ref)	5.7 (4.6 to 7.1)	32.6 (26.3 to 40.4)
Among NIS Hospitalizations for ULDAE According to Race*			
Hospitalizations for ULDAE with SJS/TEN, N (%)	175 (29)	155 (26)	163 (27)
Hospitalizations for ULDAE without SJS/TEN, N (%)	10,012 (60)	2,940 (18)	987 (6)
Crude OR (95% CI)	1.00 (Ref)	2.9 (1.8 to 4.7)	8.3 (5.0 to 13.7)
Age-Sex-Adjusted OR (95% CI)	1.00 (Ref)	2.8 (1.7 to 4.6)	8.5 (5.1 to 14.0)
Age-Sex-CAD-CKD-Diabetes-Adjusted OR (95% CI)	1.00 (Ref)	2.8 (1.7 to 4.5)	8.1 (5.0 to 13.3)

SJS/TEN = Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis; ULDAE = Urate-Lowering Drug Adverse Event

CAD = coronary artery disease; CKD = chronic kidney disease

* Hispanics, other races, and those with missing race data are not reported as their unweighted cell size was 10 or fewer, in which case individual group reporting is not allowed according to the Healthcare Cost and Utilization Project Data Use Agreement.