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Drug Hypersensitivity Reactions Documented in Electronic Health Records within a Large Health System

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Abstract

Background: Hypersensitivity reactions (HSRs) are immunologic responses to drugs. Identification of HSRs documented in the electronic health record (EHR) is important for patient safety.

Objective: To examine HSR epidemiology using longitudinal EHR data from a large United States healthcare system.

Methods: Patient demographic information and drug allergy data were obtained from the Partners Enterprise-wide Allergy Repository (PEAR) for two large tertiary care hospitals from 2000 to 2013. Drug-induced HSRs were categorized into immediate and delayed HSRs based on typical phenotypes. Causative drugs and drug groups were assessed. The prevalence of HSRs were determined, and sex and racial differences were analyzed.

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Results—Among 2.7 million patients, 377,474 (13.8%) reported drug-induced HSRs, of which 70.3% were female and 77.5% were white. A total of 580,456 HSRs were reported, of which 53.1% were immediate reaction phenotypes. Common immediate HSRs included hives (48.8%), itching (15.0%) and angioedema (14.1%). Delayed HSR phenotypes (46.9%) were largely rash (99.0%). Pencillins were associated with the most immediate (33.0%) and delayed (39.0%) HSRs. While most HSRs were more prevalent in females and white patients, notable differences were identified for certain rare HSRs including acute interstitial nephritis, which appeared more commonly in males (0.02% vs. 0.01%, $p<0.001$). Asian patients had more fixed drug eruptions (0.007% vs. 0.002%, $p=0.021$) and severe cutaneous adverse reactions (0.05% vs. 0.04%, $p<0.001$).

Conclusion—Drug HSRs were reported in 13.8% of patients. Almost one-half of reported immediate HSR phenotypes were hives and almost all reported delayed HSR phenotypes were rash. HSRs largely affected female and white patients, but differences were identified for specific rare HSRs.

Keywords

Adverse drug event; drug allergy; drug hypersensitivity; electronic health record; epidemiology; safety

BACKGROUND

Adverse drug reactions (ADRs), unintended or noxious reactions to drugs used at normal doses, lead to hospital admission in up to 7% of adult patients and affect up to 20% of inpatients [1-3]. ADRs are associated with an increased hospital length of stay and higher patient mortality, and represent a burden to the healthcare system [4]. Documentation of ADRs and adverse event avoidance remain important to patient safety initiatives.

The United States (US) maintains large ADR registries, such as Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and the Livertox database, but the voluntary nature of this reporting does not enable ADR prevalence estimations [5-7]. While registries exist for specific drug hypersensitivity reactions (HSRs, i.e., reactions that result from immunologic responses to drugs) outside the US, such as the Registry of Severe Cutaneous Adverse Reactions (RegiSCAR) in Europe, there is no US RegiSCAR equivalent and there are limited general HSR registries internationally [8]. The prevalence of most HSRs, therefore, remains unknown.

Healthcare professionals typically enter all reaction types (e.g., hypersensitivities, intolerances, and contraindications) in the allergy section/module of the electronic health record (EHR). However, HSRs account for only 20% of ADRs [9-13]. Although large epidemiologic studies have used US EHR data, prior studies have not distinguished HSRs by phenotype using free-text entries and typical onset/timing [14-16]. We investigated HSRs documented within the EHRs of a large patient population to advance the descriptive epidemiology of HSRs in the US.

METHODS

Settings and Data Collection

We conducted an observational study using drug allergy records from the Partners Enterprise-wide Allergy Repository (PEAR) within the EHR of the Partners HealthCare System, an integrated healthcare delivery network in the Greater Boston area that includes Brigham and Women's Hospital and Massachusetts General Hospital. Patient drug allergy information in PEAR includes HSRs and other types of adverse reactions documented by healthcare team members during usual clinical care. The EHR allergy module allows entry of structured data (94%) and/or free text data (6%) [17]. In a previous study, we converted all free-text reactions to a coded format, using a natural language processing (NLP) system, called the Medical Text Extraction, Reasoning and Mapping System [18]. The results of our NLP mapping were then manually reviewed for accuracy, which resulted in 787 unique reactions.

Allergies can be updated or removed over time, as clinically appropriate. We therefore included active allergies from January 2000 to October 2013 in this study, focusing on the subset of reactions representing potentially immune-mediated reactions (i.e., HSRs). Potential HSRs were identified using coded and free-text reaction data guided by input from allergy specialists and review of published literature (see Table E1 in the Online Repository) [11,17,19]. For example, anaphylaxis included documentations of arrest, asystole, hypotension, and shock; respiratory reactions included documentations of bronchospasm, shortness of breath, and wheezing. Based on their typical latency of onset, HSRs were further classified as immediate (e.g., hives, anaphylaxis) or delayed (e.g., maculopapular rash, pneumonitis) phenotypes [11]. We excluded reactions that may be immunologic, but which required additional data to differentiate (e.g., hematologic reactions such as cytopenia, rhinitis). To increase the specificity of reaction data, we manually removed potential drug-reaction combinations more likely to be ADRs than HSRs (e.g., hypotension from beta-blockers, peripheral edema from dihydropyridine calcium channel blockers), a process informed by pharmacists and allergists. The number of drug HSRs per patient was determined by evaluating the number of unique allergy records by reaction group (e.g., immediate, delayed, both). Patient sex and race were obtained from EHR demographic tables. Length of data coverage was calculated for each patient using dates of PEAR entry and latest update.

Data Analysis

We classified causative drugs into a hierarchy of drug categories based on a commercial knowledge base (First DataBank, South San Francisco, CA). This categorization included: parent category (e.g., anti-infective agents), intermediate category (e.g., penicillins), and drug category (e.g., penicillin, penicillinase-resistant). Drug dosage and indication were used to ensure appropriate classification of drugs into their respective drug and parent category. For example, the beta-blocker timolol is available in ophthalmic and oral forms, and belongs to two different drug categories and parent categories. Intermediate categorizations excluded drug combinations, unless both drugs in the combination were a member of the intermediate category (e.g., a combination of oxycodone and acetaminophen was not included in the

opioid intermediate category because acetaminophen is not an opioid). An exception was made for antimicrobial combinations (e.g., amoxicillin-clavulanic acid, beta-lactam and beta-lactamase inhibitor).

We identified patients with any potential HSR, patients with immediate HSR phenotypes, patients with delayed HSR phenotypes, and those with both immediate and delayed HSR phenotypes. We calculated the prevalence of HSRs by sex and race, using all PEAR patients as the denominator. We compared the prevalence of specific HSRs to patients in PEAR without the HSR in question by sex and race.

Descriptive statistics were used to summarize patient characteristics and HSRs. A chi-square test or Fisher's exact test were used to compare prevalence of HSRs by patient characteristics (e.g., sex, race), as appropriate. A negative binomial regression was used to compare the number of drug HSR per patient by sex. A p-value of <0.05 was considered statistically significant. Statistical analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). This study was reviewed and approved by the Partners Institutional Review Board.

RESULTS

Patient Population

We identified 4,017,708 reactions reported by 2,734,506 patients. The duration of the allergy data coverage for this patient cohort is a total of 3,107,019,075 days (median 713 [IQR 71,896], range [1-11,991]). After excluding records not consistent with a hypersensitivity reaction or not related to a drug trigger (n=3,433,628) and records not consistent with an ADR (n=3,624), there were 377,474 (13.8%) patients who reported 580,456 potential HSRs, including 308,293 immediate HSRs reported by 215,643 (7.9%) patients, and 272,163 delayed HSRs reported by 211,761 (7.8%) patients (Table 1).

Overall, we found females had a higher prevalence of HSRs than males (17.6% vs. 9.2%, $p<0.001$) (Table 1). The HSR population was overall largely white (n=292,564, 77.5%). Black patients comprised 3.8% of patients with HSRs and represented a greater proportion of patients with an immediate HSR than delayed HSR phenotype (5.9% vs 4.2%, $p<0.001$). In contrast, Asian patients comprised a greater proportion of patients with a delayed HSR than immediate HSR phenotype (5.1% vs 4.3%, $p<0.001$).

Patients had an average of 2.7 drug HSRs, which was higher in patients with immediate HSR phenotypes than in patients with delayed HSR phenotypes (1.4 vs. 1.3, $p<0.001$). Females had more documented HSRs of all types (overall, immediate, delayed), compared to males (all $p<0.001$). Patients with both immediate and delayed HSR phenotypes were more frequently female (2.5% vs. 0.9%, $p<0.001$) and had a higher mean number of HSRs than males (3.2 vs. 2.9, $p<0.001$).

Hypersensitivity Reactions

Among the 308,293 immediate HSRs (from 215,643 patients, Table 1), hives was the most common (n=150,450, 48.8% of immediate HSRs and 25.9% of all HSRs), followed by

itching (n=46,200, 15.0% of immediate HSRs and 8.0% of all HSRs), angioedema (n=43,600, 14.1% of immediate HSRs and 7.5% of all HSRs), respiratory reactions (n=34,307, 11.1% of immediate HSRs and 5.9% of all HSRs), and anaphylaxis (n=33,736, 10.9% of immediate HSRs and 5.8% of all HSRs). Of 272,163 delayed HSRs (from 211,761 patients, Table 1), rash was the most frequently documented (n=269,493, 99.0% of delayed HSRs and 46.4% of all HSRs), followed by severe cutaneous adverse reactions (SCARs) (n=1,415, 0.5% of all delayed HSRs and 0.2% of all HSRs), serum sickness (n=521, 0.2% of all delayed HSRs and 0.09% of all HSRs), acute interstitial nephritis (AIN) (n=442, 0.2% of all delayed HSRs and 0.08% of all HSRs), pneumonitis (n=120, 0.02% of all delayed HSRs and 0.02% of all HSRs), erythema nodosum (n=86, 0.03% of all delayed HSRs and 0.01% of all HSRs), and fixed drug eruption (n=86, 0.03% of all delayed HSRs and 0.01% of all HSRs).

There was a female predominance for the majority of HSRs (Table 1), with the exceptions for certain rare delayed HSRs - i.e., AIN (204 cases or 0.02% male vs. 177 cases or 0.01% females, $p<0.001$) and fixed drug eruptions (42 cases or 0.003% in males vs. 36 cases or 0.002% in females, $p=0.132$).

White patients accounted for the majority of immediate and delayed HSRs (Table 1). Black patients accounted for more documentations of respiratory reactions (4.5%, $p<0.001$) and angioedema (5.9%, $p<0.001$) than represented in the overall population (3.8%). Angioedema cases were not differential between White patients and Black patients (1.5 vs. 1.4%, $p=0.98$). In evaluating only angiotensin-converting enzyme inhibitors (ACEI) and angioedema, Black patients had a significantly higher prevalence, compared to the PEAR population (456 cases identified, 0.003% vs. 2,086 cases, 0.0008%, $p<0.001$). Asian patients represented 2.1% of the population, but 4.5% of patients with a SCAR HSR (50 cases identified).

Of the 1,415 SCARs identified (from 1,122 patients), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) accounted for most of these reactions (73.9%, n=1,056) with 755 patients reporting SJS and 77 patients reporting TEN. Black patients appeared somewhat overrepresented for DRESS (5 cases identified, 0.003% vs. non-Black: 48 cases identified, 0.002%; $p<0.05$), SJS (42 cases identified, 0.027% vs. non-Black: 646 cases identified, 0.028%, $p<0.05$) and TEN (9 cases identified, 0.006% vs. non-Black: 55 cases identified, 0.002%, $p<0.05$) (Table 2). Asian patients appeared somewhat overrepresented for acute generalized exanthematous pustulosis (AGEP) (28.6%), DRESS (5.5%), SJS (4.4%) and TEN (7.8%). In comparing to the PEAR population, Asian patients had a higher prevalence of DRESS, SJS, and TEN (all $p<0.001$).

Attributed Drugs

For most intermediate drug categories, hives was the most commonly documented HSR, with the exceptions of angioedema for ACEI and itching for opioids. Rash was the most commonly documented reaction for all intermediate drug categories in the delayed HSR group, accounting for over 96% of the delayed HSRs for each intermediate category. Anti-infective drugs were reported to be the causative agent for the majority of SCARs (936 out of 1,415, 66.1%).

Penicillins were the intermediate drug category that accounted for the largest proportion for most immediate HSRs (Figure 1). Other common culprits were sulfonamide antibiotics, opioids, NSAIDs, and ACE inhibitors. Penicillins also accounted for the largest proportion for most delayed HSRs, with sulfonamide antibiotics also common (Figure 2). SCAR culprits included sulfonamide antibiotics, penicillins, and anticonvulsants, but also cases from ACE inhibitors, antidepressants, cephalosporins, fluoroquinolones, macrolides, and NSAIDs.

Natural penicillins were the most common drug category resulting in each type of immediate HSR (see Table E2 in the Online Repository). Similarly, sulfonamide antibiotics were the second most common drug category associated with each type of immediate HSR. The delayed HSRs had a greater variety of drug categories that resulted in each type of HSR, with natural penicillins the most common for rash (81,219 out of 269,493, 30.1%) and serum sickness (149 out of 521, 28.6%), while sulfonamide antibiotics most commonly documented for SCAR (360 out of 1,415, 25.4%) and fixed drug eruption (21 out of 86, 24.4%) (see Table E3 in the Online Repository). The most common drug category for erythema nodosum was tetracycline antibiotics (15 out of 86, 17.4%), while methotrexate (27 out of 120, 22.5%) and penicillinase-resistant penicillins (89 out of 442, 20.1%) accounted for the most pneumonitis and AIN HSRs, respectively.

DISCUSSION

We used methodologies based in informatics to identify documented HSRs within our health system's EHR, and found that 13.8% of the population reported one or more HSR and that females generally had more HSRs than males. We identified a higher prevalence of all common HSRs in females than males, but rare, delayed HSR phenotypes were more balanced between sexes. While most HSRs were reported in white patients, Asian patients appeared somewhat overrepresented in rare delayed HSR phenotypes including SCAR. Hives were the most common immediate HSR and rash was the most common delayed HSR. Anti-infective agents were the most common drug category implicated in causing HSRs with natural penicillins being the most common drug category reported to cause immediate HSRs (88.9%) and sulfonamide antibiotics being the most common cause of delayed HSRs (85.7%). Tetracyclines were the most prominent causative agents for drug-induced erythema nodosum and sulfonamide antibiotics were the most prominent cause of fixed drug eruption.

We found that cutaneous reactions comprised a majority (56.1%) of all HSRs. Prior studies have similarly found that cutaneous reactions are common; dermatologic ADRs were identified to be the most common type of ADRs that was treated in the emergency department (26.3%) [20]. Except for rash, delayed HSR phenotypes were uncommon, as expected. Although rare, there is substantial patient morbidity associated with these HSRs, and they carry a high cost of medical care. SCARs have been associated with mortality rates up to 20%, with deaths often occurring from sepsis [22,23]. AIN requires dialysis in up to one-third of patients [24]. Despite the severity of these immunologic reactions, it is notable that SCARs are exclusively documented by free-text entry in most EHR systems [17]. Given that these HSRs most often represent absolute contraindications to receiving the same drug -- and often even similar, potentially cross-reactive drugs -- these reactions should be entered

as coded data to ensure the appropriate triggering of clinical decision support and transferring of allergy information between systems to ensure patient safety.

Most HSRs identified were more common in females than males. This is similar to prior studies assessing adverse reactions which found females were more likely to report a drug allergy generally [14-16,25,26]. The difference in HSR frequency between sexes was most notable for the cutaneous reactions, such as itching and hives. While it is not known why females report more drug allergy than males, this sex differential is notably absent in prior pediatric populations studied [27,28]. The observed sex difference in adults that we found may be due to comorbid multiple drug allergy syndrome [26]. Erythema nodosum, which can be medication-induced or autoimmune, occurs five times more often in female patients than male patients [29,30]. In this study, the rare delayed HSRs were largely balanced with only one HSR (AIN) having a higher prevalence in males than females, which corroborates prior studies that identified AIN (and acute renal failure generally) as being more common in males than females [31,32].

We found an overrepresentation of HSRs with certain racial groups, such as Black patients and angioedema, and Asian patients and SCARs. Despite the overrepresentation of Black patients and angioedema, we did not find a significant difference in prevalence except for the subpopulation of ACEI-induced angioedema, which is a known risk in Black patients [33,34]. The disproportionate representation of Asians and SCARs may be related to pharmacogenomics; for example, the HLA-B*1502 allele is associated with carbamazepine-induced SJS in Han Chinese, with all patients who experienced SJS having this allele [35,36]. However, despite this overrepresentation of SCAR in Asian patients, we did not find a significant difference in prevalence [37]. Yet, with access to this large number of patients and reproducible informatics methods that can identify potential SCAR patients, SCAR research in the US may be able to assess SCAR risk in Black, Hispanic, and other minority populations. However, our SCAR cases have not been validated to date. Prior SCAR validation using an extensive keyword search on EHR allergy list [20] and diagnostic codes [38] has demonstrated low (13-14%) validation.

The causative drugs for HSRs identified in this study were consistent with prior studies of drug allergy in the EHR [14,39]. While we found that penicillins were a primary cause of angioedema, prior studies identified angiotensin receptor antagonists and NSAIDs as the most common causes of angioedema [40]. ACEI angioedema accounts for approximately 30% of all angioedema-related admission to the emergency department [41]. Antibiotics and beta-lactams specifically, have been implicated in causing approximately half of anaphylaxis cases in the Allergy Vigilance Network [42,43]. Although nitrofurantoin is generally thought to be the most common cause of pneumonitis [44,45], it was the second most common cause in our study (23 cases), with methotrexate identified as the most common cause (27 cases). Antibiotics, including beta-lactams, account for one-third of drug-related AIN [46]. Proton pump inhibitors, which we found as the fourth most common drug category causing AIN behind penicillins and sulfonamides, have been previously known to cause AIN, especially in elderly patients [47]. Antibiotics and anticonvulsants have considered the most common causes of SCARs [22,48,49], and similarly, we found that antibiotics caused 72.8% of reported SCAR cases. We confirmed that sulfonamide antibiotics were the most common

cause of documented fixed drug eruption (with NSAIDs similarly prominent) and identified tetracyclines as a commonly documented drug-induced erythema nodosum culprit.

Our study has several notable limitations. First, HSRs represent reported reactions in the EHR, grouped using reaction data entered by clinicians in the allergy module of the EHR only. HSRs were not validated with laboratory testing, biopsies, skin testing, or other diagnostic techniques. For example, although 29,486 patients had documented anaphylaxis, cases were previously noted to be rarely confirmed with serum tryptase testing (<1%) [50]. However, we used all reaction text and phenotype groupings established by experts and previously implemented [14,17,25]. In order to group HSRs, we assumed typical temporal onset of HSRs considering the symptoms and signs in the EHR allergy record to be a clinical phenotype, but we did not have timing of onset information in the EHR. Thus, for example, we grouped all rash without any further specifications as a delayed HSR phenotype, which are more common than immunoglobulin E (IgE)-mediated cutaneous reactions. We were unable to distinguish rash mechanisms, and considered patients with reactions consistent with immediate HSR phenotypes together, although many of these patients may have non-IgE-mediated mast cell activation rather than IgE-mediated drug allergy [51,52]. Although we include patients' self-reported race in this analysis, HSR risk may be more related to ethnicity than race, a factor unavailable for analysis [53,54]. There were some HSRs with a very small prevalence (e.g., SCAR) that may limit the findings of our sex/race evaluation. Although patient age at the time of HSR is important to assess, our records indicate only the current age of the patient, not the age of the patient when the HSR occurred. Finally, while our study comes from one US health system, and findings may not be generalizable to other US or international populations, we included allergy data from over 2.7 million patients over more than a decade.

CONCLUSIONS

We described the epidemiology of documented drug HSRs within a large health system, illustrating common HSRs and their causative drugs. Our study provides a greater understanding of the prevalence of HSRs by patient-specific factors in a more geographically representative sample than current literature. Improved allergy documentation and clinical decision support is needed, especially for the rare, delayed HSR phenotypes, to facilitate future drug hypersensitivity research and improve patient safety.

Extended Data

Table E1.

Hypersensitivity reaction definitions and method of identification in the electronic health record

Reaction name	Coded text	Free text keywords
<i>Immediate Hypersensitivity Reactions</i>		
Itching	Itching	Itching, itching eyes, itching in mouth, itching of eyes
Hives	Hives	Hives, urticaria

Reaction name	Coded text	Free text keywords
Respiratory	Bronchospasm; bronchospasm or wheezing; shortness of breath; wheezing	Bronchospasm; wheezing; shortness of breath, breathing difficulty, respiratory distress; airway closure, airway constriction, apnea; asthma, asthma attack, asthma exacerbation, asthma flare, asthmatic reaction
Angioedema	Angioedema; swelling	Angioedema, swelling, throat edema, tongue edema, lip edema; lip swell, swollen eye(s), and swollen face
Anaphylaxis	Anaphylaxis; hypotension	Anaphylaxis, anaphylactic reaction, anaphylactic shock; asystole, cardiac arrest, cardiopulmonary arrest; hypotension, hypotensive, low blood pressure; shock
Delayed Hypersensitivity Reactions		
Rash	Hives or other rash; rash	Rash, allergic contact dermatitis, allergic dermatitis, atopic dermatitis, blistering rash, rash around mouth, rash in mouth, skin eruption, skin eruptions
Fixed drug Eruption	N/A	Fixed drug eruption, fixed drug reaction
Erythema nodosum	N/A	E nodosum, erythema nodosum
Serum sickness	N/A	Serum reaction, serum sickness
Pneumonitis	N/A	Allergic pneumonitis, hypersensitivity pneumonia, hypersensitivity pneumonitis, pneumonitis
Acute interstitial nephritis	N/A	Acute interstitial nephritis, AIN, allergic interstitial nephritis, interstitial nephritis
Severe cutaneous adverse reaction	N/A	Acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; E multiforme, erythema multiforme; SJS, Steven Johnson syndrome; TEN, toxic epidermal necrolysis; desquamation, severe skin reaction

N/A: no coded entry available for these reactions in electronic health record at time of data collection

Table E2.

Immediate Hypersensitivity Reaction and Top Five Causative Drugs by Drug Category

Rank	Itching (n=46,200)	Hives/ Urticaria (n=150,450)	Respiratory (n=34,307)	Angioedema/ Swelling (n=43,600)	Anaphylaxis/Arrest/Asystole/ Hypotension/Shock (n=33,736)
1	PCN – Natural ^a (6,544, 14.2)	PCN – Natural ^a (51,325, 34.1)	PCN – Natural ^a (5,600, 16.3)	PCN – Natural ^a (9,568, 21.9)	PCN – Natural ^a (11,236, 33.5)
2	Sulfa ABX/ SMX-TMP (5,709, 12.4)	Sulfa ABX/ SMX-TMP (28,491, 18.9)	Sulfa ABX/ SMX-TMP (3,247, 9.5)	Sulfa ABX/ SMX-TMP (5,602, 12.8)	Sulfa ABX/ SMX-TMP (3,953, 11.8)
3	Analgesic Narcotic Agonists ^b (5,591, 12.1)	Aminopenicillin Antibiotic ^d (10,132, 6.7)	Analgesic Narcotic Agonists ^b (3,114, 9.1)	NSAID (COX Non-Specific) ^e (3,343, 7.7)	Analgesic Narcotic Agonists ^b (2,128, 6.4)
4	Analgesic Narcotic Oxycodone Combinations ^c (3,000, 6.5)	NSAID (COX Non-Specific) ^e (5,112, 3.4)	NSAID (COX Non-Specific) ^e (2,312, 6.7)	ACE Inhibitors (2,751, 6.3)	NSAID (COX Non-Specific) ^e (1,675, 5.0)
5	Fluoroquinolone (1,619, 3.5)	Analgesic Narcotic Agonists ^b	ACE Inhibitors (1,544, 4.5)	Fluoroquinolone (1,533, 3.5)	Fluoroquinolone (1,046, 3.1)

Rank	Itching (n=46,200)	Hives/ Urticaria (n=150,450)	Respiratory (n=34,307)	Angioedema/ Swelling (n=43,600)	Anaphylaxis/Arrest/Asystole/ Hypotension/Shock (n=33,736)
		(3,930, 2.6)			

ABX = antibiotic; ACE = angiotensin-converting enzyme; COX = cyclooxygenase; NMB = neuromuscular blocker; NSAID = non-steroidal anti-inflammatory drugs; PCN = penicillin; SMX-TMP = sulfamethoxazole-trimethoprim

^aIncludes penicillin G, penicillin V

^bIncludes morphine, oxycodone

^cIncludes oxycodone-acetaminophen

^dIncludes amoxicillin, ampicillin

^eIncludes ibuprofen, naproxen

Table E3.

Non-immediate Hypersensitivity Reaction and Top Five Causative Drugs by Drug Category

Rank	Dermatitis/Rash (n=269,493)	Fixed drug eruption (n=86)	Erythema nodosum (n=86)	Serum sickness (n=521)	Pneumonitis (n=120)	AIN (n=442)	SCAR (n=1,415)
1	PCN – Natural ^a (81,219, 30.1)	Sulfa ABX/ SMX-TMP (21, 24.4)	Tetracycline Antibiotics (15, 17.4)	PCN – Natural ^a (149, 28.6)	Methotrexate (27, 22.5)	PCN - Penicillinase- resistant ^h (89, 20.1)	Sulfa ABX/ SMX-TMP (360, 25.4)
2	Sulfa ABX/ SMX-TMP (55,916, 20.7)	NSAID (COX Non-Specific) ^c (16, 18.6)	PCN – Natural ^a (13, 15.1)	Sulfa ABX/ SMX-TMP (81, 15.5)	Urinary Antibacterial - Nitrofurantoin ^e Derivatives ^e (23, 19.2)	PCN – Natural ^a (54, 12.2)	PCN – Natural ^a (169, 11.9)
3	Aminopenicillin Antibiotic ^b (19,724, 7.2)	Antifungal Triazoles ^d (9, 10.5)	Sulfa ABX/ SMX-TMP (12, 14.0)	Aminopenicillin Antibiotic ^b (60, 11.5)	Antineoplastic - Taxanes (13, 10.8)	Sulfa ABX/ SMX-TMP (46, 10.4)	Anticonvulsant - Phenyltriiazepine Derivatives ⁱ (69, 4.9)
4	Fluoroquinolone (7,879, 2.9)	Fluoroquinolone (8, 9.3)	Oral Contraceptive (10, 11.6)	Cephalosporin Antibiotics -2nd Generation ^f (31, 6.0)	Anti- arrhythmic- Class III ^f (6, 5.0)	PPI (46, 10.4)	Aminopenicillin Antibiotic ^b (67, 4.7)
5	Tetracycline Antibiotics (6,345, 2.4)	Tetracycline Antibiotics (6, 7.0)	Fluoroquinolone (3, 3.5)	Tetracycline Antibiotics (30, 5.8)	Antineoplastic - Antiandrogens ^g (3, 2.5)	Fluoroquinolone (31, 7.0)	Anticonvulsant - Hydantoins ^j (57, 4.0)

ABX = antibiotic; AIN = acute interstitial nephritis; PCN = penicillin; PPI = proton pump inhibitor; SCAR = severe cutaneous adverse reaction; SMX-TMP = sulfamethoxazole-trimethoprim

^aIncludes penicillin G, penicillin V

^bIncludes amoxicillin, ampicillin

^cIncludes ibuprofen, naproxen

^dIncludes fluconazole, voriconazole

^eIncludes nitrofurantoin

^fIncludes amiodarone, dofetilide

^gIncludes bicalutamide, nilutamide

^hIncludes nafcillin, oxacillin

ⁱIncludes lamotrigine

^jIncludes fosphenytoin, phenytoin

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Declarations

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Abbreviations

ACEI	angiotensin-converting enzyme inhibitors
ADE	adverse drug event
ADR	adverse drug reaction
AGEP	acute generalized exanthematous pustulosis
AIN	acute interstitial nephritis
DRESS	drug reaction with eosinophilia and systemic symptoms
EHR	electronic health record
EM	erythema multiforme
HSR	hypersensitivity reaction
NLP	natural language processing
NSAIDs	non-steroidal anti-inflammatory drugs
SCAR	severe cutaneous adverse reactions
SJS	Stevens-Johnson syndrome
TEN	toxic epidermal necrolysis

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Highlights

What is already known about this topic?

Hypersensitivity reactions (HSRs) account for 20% of adverse drug reactions, which are associated with patient outcomes such as hospital length of stay, morbidity and mortality.

What does this article add to our knowledge?

Using allergy records derived from usual patient care in an electronic health record, we found that 13.8% of patients experience an HSR. Comparisons of the prevalence of HSRs by sex and race were evaluated.

How does this study impact current management guidelines?

This study helps quantify the prevalence of HSRs by sex and race, including in minority populations in the United States. Understanding drug-induced hypersensitivity reactions can improve prescribing and documentation of allergies in patient records.

Figure 1. Distribution of immediate hypersensitivity reactions by intermediate medication category.

In this figure, the most common drug class culprits reported to cause immediate hypersensitivity reactions are displayed. The y-axis demonstrated the percentage of each immediate HSR that was attributed to each drug class, noted by color. The five most common drug categories causing immediate HSRs are also displaced in Additional file 1: Table S2. AIN = acute interstitial nephritis; NSAIDs = non-steroidal anti-inflammatory drugs

Figure 2. Distribution of delayed hypersensitivity reactions by intermediate medication category

In this figure, the most common drug class culprits reported to cause delayed hypersensitivity reactions are displayed. The y-axis demonstrated the percentage of each immediate HSR that was attributed to each drug class, noted by color. The five most common drug categories causing delayed HSRs are also displaced in Additional file 1: Table S3 ACE = angiotensin converting enzyme; AIN = acute interstitial nephritis; NSAIDs = non-steroidal anti-inflammatory drugs; SCAR = severe cutaneous adverse reactions

Table 1.

Prevalence of reported hypersensitivity reactions (HSRs) by patient demographic characteristics and by HSR phenotype among a total of 2,734,506 patients; 377,474 patients reported 580,456 HSRs.*

	Total n (%) ^a	Sex n (%) ^a		Racial/ethnic group ^d n (%) ^a					
		Female (n=1,511,555)	Male (n=1,222,649)	White ^e (n=1,814,521)	Black ^f (n=156,892)	Hispanic ^g (n=171,071)	Asian ^h (n=94,332)	Other ⁱ (n=47,028)	
Patients with HSRs	377,474 (13.8)	265,539 (17.6)	111,915 (9.2)	292,564 (16.1)	14,230 (9.1)	13,828 (8.1)	8,075 (8.6)	4,178 (8.9)	
Immediate HSR Phenotypes									
Itching	215,643 (7.9)	154,536 (10.2)	61,093 (5.0)	165,619 (9.1)	9,245 (5.9)	7,577 (4.4)	4,053 (4.3)	2,272 (4.8)	
Hives	37,562 (1.4)	28,395 (1.9)	9,162 (0.7)	28,164 (1.6)	2,443 (1.6)	1,793 (1.0)	781 (0.8)	461 (1.0)	
Respiratory reactions	118,828 (4.3)	85,984 (5.7)	32,834 (2.7)	91,446 (5.0)	4,009 (2.6)	3,476 (2.0)	2,083 (2.2)	1,160 (2.5)	
Angioedema	23,204 (0.8)	17,249 (1.1)	5,954 (0.5)	18,245 (1.0)	1,047 (0.7)	909 (0.5)	438 (0.5)	239 (0.5)	
Anaphylaxis	36,217 (1.3)	26,043 (1.7)	10,173 (0.8)	27,583 (1.5)	2,131 (1.4)	1,638 (1.0)	747 (0.8)	438 (0.9)	
	29,486 (1.1)	20,620 (1.4)	8,865 (0.7)	23,779 (1.3)	995 (0.6)	910 (0.5)	423 (0.4)	307 (0.7)	
Delayed HSR Phenotypes									
Rash	211,761 (7.7)	149,013 (9.9)	62,727 (5.1)	163,237 (9.0)	6,578 (4.2)	7,896 (4.6)	4,845 (5.1)	2,357 (5.0)	
Fixed drug eruption	210,162 (7.7)	148,090 (9.8)	62,050 (5.1)	162,033 (8.9)	6,500 (4.1)	7,853 (4.6)	4,784 (5.1)	2,341 (5.0)	
Erythema nodosum	78 (0.003)	36 (0.002)	42 (0.003)	51 (0.003)	6 (0.004)	3 (0.002)	7 (0.007)	1 (0.002)	
Serum sickness	77 (0.003)	72 (0.005)	5 (0.0)	60 (0.003)	2 (0.001)	2 (0.001)	2 (0.002)	0	
Pneumonitis	497 (0.02)	345 (0.02)	152 (0.01)	401 (0.02)	9 (0.01)	10 (0.01)	6 (0.01)	4 (0.01)	
AIN	96 (0.004)	65 (0.004)	31 (0.003)	86 (0.005)	0	0	2 (0.002)	1 (0.002)	
SCAR	381 (0.01)	177 (0.01)	204 (0.02)	295 (0.02)	34 (0.02)	11 (0.01)	9 (0.01)	7 (0.01)	
	1,122 (0.04)	674 (0.04)	448 (0.04)	824 (0.05)	57 (0.04)	37 (0.02)	50 (0.05)	15 (0.03)	
Both Immediate and Delayed HSR Phenotypes									
	49,930 (1.8)	38,772 (2.5)	11,158 (0.9)	40,193 (2.2)	1,764 (1.1)	1,821 (1.1)	911 (1.0)	499 (1.1)	

AIN = acute interstitial nephritis; PEAR = Partners Enterprise-wide Allergy Repository; SCAR = severe cutaneous adverse reaction

* Percentage is prevalence of HSR among the entire population in PEAR; columns may add up to greater than 100% as patients may have had multiple HSR by HSR group

^a Denominator used is patients in PEAR that are part of group (i.e., by column)

^b Sex information for patients with an HSR was missing for 302 patients

^c All HSRs comparing females and males were significantly ($p<0.05$) more prevalent among females than males, except for AIN, which was significantly more prevalent ($p<0.05$) among males than females, and fixed drug eruption ($p>0.05$)

^d Race information for patients with an HSR was missing (e.g., unknown, refused) for 44,599 patients

^e White patients had a significantly ($p<0.05$) higher prevalence of all HSRs, compared to the rest of the PEAR population

^f Black patients had a significantly ($p<0.05$) higher prevalence of itching, compared to the rest of the PEAR population; Black patients had a significantly ($p<0.05$) lower prevalence of HSRs; immediate HSRs, hives, respiratory reactions, anaphylaxis; delayed HSRs, rash, serum sickness, SCAR; and both immediate and delayed HSRs, compared to the rest of the PEAR population

^g Hispanic patients had a significantly ($p<0.05$) lower prevalence of HSRs; immediate HSRs, itching, hives, respiratory reactions, angioedema, anaphylaxis; delayed HSRs, rash, serum sickness, AIN, SCAR; and both immediate and delayed HSRs, compared to the rest of the PEAR population

^h Asian patients had a significantly ($p<0.05$) higher prevalence of fixed drug eruption, compared to the rest of the PEAR population; Asian patients had a significantly ($p<0.05$) lower prevalence of HSRs; immediate HSRs, itching, hives, respiratory reactions, angioedema, anaphylaxis; delayed HSRs, rash, serum sickness, SCAR; and both immediate and delayed HSRs, compared to the rest of the PEAR population

ⁱ Other patients had a significantly ($p<0.05$) lower prevalence of HSRs; immediate HSRs, itching, hives, respiratory reactions, angioedema, anaphylaxis; delayed HSRs, rash; and both immediate and delayed HSRs, compared to the rest of the PEAR population

Table 2.

Prevalence of reported drug-induced severe cutaneous adverse reactions by patient demographic characteristics

	Total n (%)	Sex ^a n (%)		Racial/ethnic group ^b n (%)				
		Female ^c n=1,511,555	Male n=1,222,649	White ^d n=1,814,521	Black ^e n=156,892	Hispanic ^f n=171,071	Asian ^g n=94,332	Other n=47,028
Patients with SCAR	n=2,734,506							
AGEP	1,122 (0.04)	674 (0.05)	448 (0.04)	824 (0.05)	57 (0.04)	37 (0.02)	50 (0.05)	15 (0.03)
	7 (0.0)	4 (0.0)	3 (0.0)	5 (0.0)	0	0	2 (0.0)	0
DRESS	55 (0.002)	33 (0.002)	22 (0.002)	41 (0.002)	5 (0.003)	4 (0.002)	3 (0.003)	0
EM	259 (0.009)	135 (0.009)	124 (0.01)	176 (0.01)	5 (0.003)	10 (0.006)	8 (0.008)	5 (0.001)
SJS	755 (0.03)	481 (0.03)	274 (0.02)	582 (0.03)	42 (0.03)	22 (0.01)	33 (0.04)	9 (0.02)
TEN	77 (0.003)	44 (0.003)	33 (0.003)	45 (0.002)	9 (0.006)	3 (0.002)	6 (0.006)	1 (0.002)

AGEP = acute generalized exanthematous pustulosis; DRESS = drug reaction with eosinophilia and systemic symptoms; EM = erythema multiforme; SCAR = severe cutaneous adverse reaction; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis

^aSex information for patients with an HSR was missing for 302 patients

^bRace information for patients with an HSR was missing (e.g., unknown, refused) for 44,599 patients

^cSCAR and SJS were significantly ($p<0.05$) more prevalent in females than males

^dWhite patients had a significantly ($p<0.05$) higher prevalence of SCAR and all subtypes, except for AGEP ($p>0.05$), compared to the rest of the PEAR population

^eBlack patients had a significantly ($p<0.05$) higher prevalence of DRESS and TEN, compared to the rest of the PEAR population; Black patients had a significantly ($p<0.05$) lower prevalence of SCAR, EM, and SJS, compared to the rest of the PEAR population

^fHispanic patients had a significantly ($p<0.05$) higher prevalence of DRESS, compared to the rest of the PEAR population; Hispanic patients had a significantly ($p<0.05$) lower prevalence of SCAR, EM, SJS, and TEN compared to the rest of the PEAR population

^gAsian patients had a significantly ($p<0.05$) higher prevalence of SCAR, DRESS, SJS, and TEN, compared to the rest of the PEAR population; Asian patients had a significantly ($p<0.05$) lower prevalence of EM, compared to the rest of the PEAR population