

Utility of *ICD-9-CM* Codes for Identification of Allergic Drug Reactions



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What is already known about this topic? Identifying cases of allergic drug reactions by *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes is a potentially valuable approach for gaining insight into the epidemiology of drug allergy, but the accuracy of the coding is unknown because previous studies were not validated by chart review.

What does this article add to our knowledge? We used chart review to better understand specific *ICD-9-CM* and E codes that identify patients with allergic drug reactions treated in the emergency department; we also identified the most common causative agents.

How does this study impact current management guidelines? This study provides a more accurate estimate of the incidence of allergic drug reactions in the emergency department and identifies readily available diagnostic codes that may be used for further study.

BACKGROUND: The epidemiology of allergic drug reactions is poorly understood due, in large part, to difficulty in identifying true cases in population data sets. Use of *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes is a potentially valuable approach that requires formal evaluation.

OBJECTIVE: To better understand the utility of *ICD-9-CM* codes for identification of allergic drug reactions, including the validation of specific codes by chart review.

METHODS: We reviewed randomly sampled medical records of patients treated in the emergency department (ED) between January 1, 2001, and December 31, 2006, with *ICD-9-CM* codes for drug allergy and E codes (E930-949) for adverse drug reactions.

RESULTS: During the 6-year period, 11,130 charts were identified by *ICD-9-CM* and E codes and 1,634 were reviewed. Allergic drug reactions were found in 444 (27%) of the reviewed ED visits. The codes that identified the highest percentage of true allergic drug reactions were dermatitis due to drug (693.0; 87%), adverse reaction to drug (995.2; 52%), and anaphylaxis (995.0; 38%). Patients with both an *ICD-9-CM* code and an E code had a high likelihood of having an allergic drug reaction (76%). Most allergic drug reactions were attributed to antibiotics (42%), intravenous contrast (7%), and nonsteroidal anti-inflammatory drugs (6%). The estimated frequency of allergic drug reactions increased from 0.49% of ED visits in 2001 to 0.94% in 2012.

CONCLUSIONS: Specific *ICD-9-CM* and E codes can be used in combination to identify allergic drug reactions. Further study of these codes in the inpatient and outpatient settings is necessary to better understand the utility of diagnosis codes for improving epidemiologic research on drug allergy. © 2015 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2016;4:114-9)

Key words: International Classification of Diseases, Ninth Revision, Clinical Modification (*ICD-9-CM*) codes; Adverse drug reactions; Drug allergy; Drug hypersensitivity; Epidemiology; Emergency department

Although exact numbers are lacking, adverse drug reactions (ADRs) are estimated to account for 3% to 6% of all hospital admissions and to occur in 10% to 15% of hospitalized patients; they result in morbidity, prolonged hospitalization, and increased risk of mortality.¹ Although most of these reactions are due to predictable and dose-dependent effects of drugs, 10% to 20% of ADRs, including allergic drug reactions, are unpredictable and dose-independent. To date, there have been few studies systematically assessing the epidemiology of drug allergy because it

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Abbreviations used

ADR- adverse drug reaction

ED- emergency department

ICD-9-CM- International Classification of Diseases, Ninth
Revision, Clinical Modification

NEISS-CADES- National Electronic Injury Surveillance System—
Cooperative Adverse Drug Event Surveillance
database

is difficult to identify true cases in population data sets.²⁻⁵ Chart review is the most complete method for case identification, but it is time consuming and resource intensive. Using diagnostic codes to improve identification of drug allergy cases is a potentially valuable approach for future research.

Clinical epidemiology studies increasingly rely on electronic medical records, including the associated billing codes. *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes are used to record the diagnosis for all patient encounters, and the validity of these codes plays a critical role in the accuracy of these studies.^{6,7} Limitations of diagnostic codes include incomplete or inaccurate information because code assignment relies on the potentially heterogeneous coding of individual physicians and their associated billing staff. ICD-9-CM codes have been used for case identification in many specialties, and researchers have found that specific conditions are often distributed across multiple codes.⁷⁻⁹ For example, the sensitivity of the most common ICD-9-CM codes listed for patients with laboratory-confirmed pneumococcal pneumonia ranged from 11% to 58%, and the sensitivity of claims-based algorithms ranged from 48% to 66% in identifying cases of pneumonia.^{8,9} In a study of emergency department (ED) patients with food and insect sting allergy, specific ICD-9-CM codes identified only 53% of the patients with food allergy, but 87% of the patients with insect sting allergy.¹⁰ The remaining patients for both types of reactions were coded with less specific allergy codes and were identified only after manual chart review.

Previous studies have tried to create algorithms to identify allergic drug reactions. For example, a study in children seen in the ED for drug-related anaphylaxis used a combination of drug-specific ICD-9-CM codes and codes for anaphylaxis, symptoms of anaphylaxis, or shock.⁴ The drug-specific codes included E codes for ADRs as well as the seemingly most specific codes for allergic drug reactions: dermatitis due to drugs and medicines taken internally (693.0) and unspecified adverse effect due to unspecified drug (995.2). E codes are a supplemental group of codes for external causes of injury that were designed to capture data for research and are not primary diagnosis codes. There are specific E codes for ADRs by type of drug. Using a database of more than 1 million visits to South Carolina EDs, this method identified only 50 children with probable or possible drug-related anaphylaxis and likely missed a significant number of patients in which a single code or less specific codes were used. Only identified patients were reviewed to confirm the reaction. Another study using data from ED visits in Florida also used a combination of ICD-9-CM codes to identify patients with drug-related anaphylaxis.² Anaphylactic drug reactions were identified by using a combination of drug allergy codes, including 693.0 and 995.2, as well as the code for shock due to anesthesia (995.4)

and E codes for antibiotics in combination with codes for anaphylaxis or symptom-specific codes. Although this method identified 157 cases of anaphylactic drug reactions, the codes were not validated with chart review. In a large retrospective study in a national database, patients with drug-induced anaphylaxis were identified with the ICD-9-CM code specific for anaphylactic shock in conjunction with a drug hypersensitivity-specific code, including 693.0, 995.2, and 995.4, and E codes for antibiotics.³ This identified 716 patients, but these were not confirmed by chart review.

Our objective was to evaluate a broad set of ICD-9-CM and E codes to better understand the utility of each code in identifying cases of drug allergy seen in the ED, to validate these codes with chart review, and then to use these findings to estimate the epidemiology of drug allergy in our ED.

METHODS

To study the accuracy of ICD-9-CM codes for identifying cases of allergic drug reactions, we reviewed random samples of medical records of adults (age, ≥ 18 years) and children (age, < 18 years) treated in our teaching hospital ED between January 1, 2001, and December 31, 2006. Records with a primary or secondary ICD-9-CM code for anaphylaxis, urticaria, angioedema, allergy, rash, pruritus, and eosinophilia were considered possible drug allergy and identified for review. The specific ICD-9-CM codes were dermatitis due to drugs and medicines taken internally (693.0), unspecified adverse effect due to unspecified drug (995.2), anaphylaxis (995.0), allergic urticaria (708.0), angioneurotic edema (995.1), allergy unspecified (995.3), specified pruritus (698.8), unspecified pruritus (698.9), rash (782.1), urticaria unspecified (708.9), and eosinophilia (288.3). In addition, we reviewed random samples of medical records for all E codes for an adverse drug event (E930-E949). Patients who had both a possible drug allergy ICD-9-CM code and an E code were included under their ICD-9-CM code. Duplicates were eliminated by allowing only 1 code per medical record number for each date.

All selected medical records were reviewed by a board-certified allergist/immunologist. Each visit was classified as an allergic drug reaction if the symptoms were temporally related to the initiation of drug therapy and were consistent with an immunologically mediated response to a drug. If necessary, notes from follow-up visits were reviewed to confirm the diagnosis. If available, the specific drug responsible for the reaction was identified. Data for age at time of the ED visit, sex, and race/ethnicity were collected at the time of chart review. For each ICD-9-CM code and E code, we determined the percentage of ED patients evaluated for allergic drug reactions.

We also obtained deidentified records for all visits by patients with a possible drug allergy ICD-9-CM code or an E code from 2007 to 2012. The number of ED visits for patients with allergic drug reaction was estimated using the number of ED visits for each code with the calculated percentage of drug allergy for that specific code.

Statistical analysis

All analyses were performed using Stata v12.0 (Stata Corp, College Station, Texas). Comparisons between patients with drug allergies and those without drug allergies were performed using Kruskal-Wallis and Fisher exact tests. A 2-tailed $P < .05$ was considered statistically significant.

TABLE I. ED visits with allergic drug reactions by *ICD-9-CM* code

Hierarchy	<i>ICD-9</i> code	<i>ICD-9</i> code description	No. of patients	No. of charts reviewed	% reviewed	No. with drug allergy	% drug allergy
1	693	Dermatitis due to drug	518	173	33.4	150	86.7
2	995.2	Adverse effect due to drug	676	119	17.6	62	52.1
3	995	Anaphylaxis	112	71	63.4	27	38.0
4	708	Allergic urticaria	624	134	21.5	33	24.6
5	995.1	Angioneurotic edema	260	69	26.5	16	23.2
6	995.3	Allergy unspecified	1073	197	18.4	22	11.2
7	698.8	Specified pruritus	72	48	66.7	13	27.1
8	698.9	Unspecified pruritus	864	85	9.8	18	21.2
9	782.1	Rash	3749	243	6.5	38	15.6
10	708.9	Urticaria unspecified	806	131	16.3	23	17.6
11	288.3	Eosinophilia	121	41	33.9	2	4.9
	E930-949	ADRs	2255	323	14.3	40	12.4
			11130	1634	14.7	444	27.2

TABLE II. Dual coding with possible drug allergy *ICD-9-CM* code and E code for ADR accurately identify visits for allergic drug reactions

	<i>ICD-9</i>	<i>ICD-9</i> + E code	E code
No. of patients	8875	860	2255
Abstracted, n (%)	1311 (14.8)	292 (34.0)	323 (14.3)
Drug allergy, n (%)	404 (30.8)	223 (76.4)	40 (12.3)

RESULTS

ICD-9 codes to identify allergic drug reactions

Over a 6-year period, using all the possible drug allergy *ICD-9-CM* and E codes, we identified 11,130 ED visits. *ICD-9-CM* codes identified 8875 visits, and adverse drug event E codes identified an additional 2225 visits.

We reviewed a total of 1311 (15%) of the 8875 visits identified by possible drug allergy *ICD-9-CM* codes (Table I). Codes specific for drug allergy most accurately identified allergic drug reactions. Specifically, 86% of the visits coded with dermatitis due to drugs (693.0) and 52% of the visits coded with unspecified adverse effect due to unspecified drug (995.2) were found to be allergic drug reactions by chart review. Between 11% and 27% of nonspecific codes such as allergy unspecified, pruritus, rash, and urticaria were found to be allergic drug reactions, and only 5% of the ED visits coded as eosinophilia (Table I). We also reviewed charts for idiopathic urticaria (708.1) and other specified urticaria (708.8), but no patients with drug allergy were identified by chart review in patients assigned these urticarial-related codes.

In addition, 323 (14%) of the 2255 visits identified by adverse drug event E codes underwent chart review (Table I). Of these 323 visits, 40 (12%) were found to have allergic drug reactions. The percentage of patients found to have drug allergy on review of E codes for specific drug classes was 39% of the visits with E codes for antibiotics (E930-931), 20% of the E codes for drugs affecting the autonomic nervous system (E941), 67% of the E codes for topical medication (E946), 30% of the E codes for unspecified drug (E947), and 25% of the E codes for other vaccine (E949). E codes for blood constituents (E934), other

central nervous system depressants and anesthetics (E938), psychotropic agents (E939), agents primarily affecting the gastrointestinal system (E943), and bacterial vaccines (E948) were found to identify visits with allergic drug reactions in 10% to 20% of the ED visits with these codes. The remaining E codes had 10% or less allergic drug reactions and were primarily ADRs including expected adverse effects.

Overall, allergic drug reactions were found in 27% of all ED visits reviewed. We found that dual coding with a relevant *ICD-9-CM* code and a relevant E code was found to have a higher likelihood of identifying an allergic drug reaction (76%) compared with coding patients with a possible drug allergy with *ICD-9-CM* code alone (31%) or an E code alone (12%) (Table II). However, only 860 (10%) of the 8875 visits identified by the *ICD-9-CM* codes were also coded with an E code, indicating that identification only by dual coding would miss 90% of allergic drug reactions.

Patient characteristics

Between January 2001 and December 2006, manual chart review of 1634 ED visits, randomly sampled from 11,130 visits identified by the *ICD-9-CM* codes detailed above, identified 444 (27%) visits by patients with confirmed allergic drug reactions. Of these patients, 373 (84%) were discharged home. Most ED visits by patients with an allergic drug reaction were by adults ($n = 392$; 88%). Patients evaluated for an allergic drug reaction were older than patients not found to have an allergic drug reaction. There were no statistically significant differences in sex or race/ethnicity between patients with and without allergic drug reactions (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Drugs causing hypersensitivity reactions

The most common cause of allergic drug reactions in both children and adults was antibiotics (44%), accounting for 42% of the reactions in adults and 60% of the reactions in children (Figure 1, A). Among antibiotics, penicillin was the most common cause in adults (32%) and in children (55%) (Figure 1, B). Reactions to intravenous contrast accounted for 7% of the allergic drug reactions in adults and gadolinium reactions for 2%. This group included patients who received

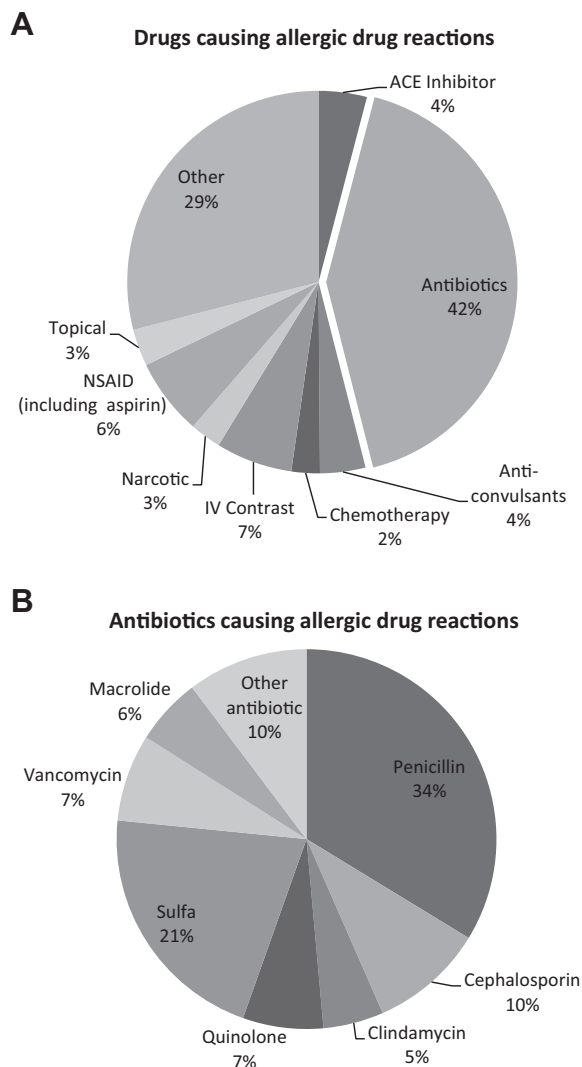


FIGURE 1. A total of 444 patients were identified with allergic drug reactions and the causative agent was determined (A). Other medications were each responsible for less than 2% of the reactions and included acetaminophen, allopurinol, antipsychotics, antivirals, COX-2 inhibitors, dapsone, gadolinium, H₂ blockers, IV iron, lasix, local anesthetics, niacin, plavix, pseudoephedrine, steroids, vaccines, and wellbutrin as well as medications that were responsible only for a single reaction. Of the patients with reactions to antibiotics, the specific antibiotic was identified (B). Other antibiotics included doxycycline, flagyl, linezolid, macrolid, minocycline, rifampin, tetracycline, and azithromycin or unspecified antibiotic. ACE, angiotensin-converting enzyme; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug.

contrast in the ED and experienced a reaction, as well as patients who were sent to the ED after a reaction to contrast that was given in an outpatient setting. Reactions to nonsteroidal anti-inflammatory drugs, including aspirin, accounted for 6% of the reactions, with most of these in adults. Angiotensin-converting enzyme inhibitor reactions were seen in 4% of adult patients, but a higher incidence was seen in black patients (12%) than in white patients (4%).

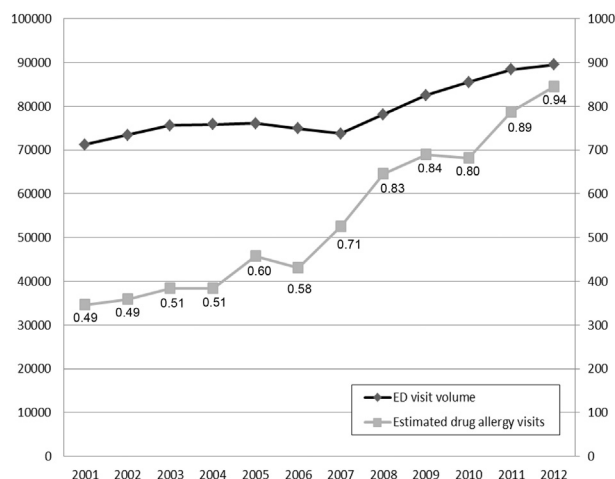


FIGURE 2. Visits for allergic drug reactions were calculated using the patients who were billed for each drug allergy ICD-9 code and E codes for ADRs and the calculated % of drug allergy for each of the codes. The estimated drug allergy visits were calculated for each year from 2001 to 2012 (right axis). The percentage of ED visits that had an allergic drug reaction was calculated using the total ED visit volume and is noted at each time point (left axis).

Drug allergy trends in the ED, 2001 to 2012

Using the prevalence data for allergic drug reactions that had been determined for each ICD-9-CM code and E codes E930-949, we determined the drug allergy trends in our ED from 2007 to 2012. The percentage of allergic drug reactions that had been determined for each relevant ICD-9-CM code was used with the ED coding data for each year to estimate the number of reactions for each ICD-9-CM code for each year. For example, there were 133 ED visits coded as 693.0 in 2007 and 86.7% of these were assumed to be due to an allergic drug reaction. The overall percentage of drug allergy in patients with E codes E930 to E949 that had been determined was used rather than the percentage for each individual drug class. Using these data, we estimated the annual number of ED visits for allergic drug reactions.

The frequency of drug allergy rose from 2001 to 2006, with allergic drug reactions accounting for an estimated 0.49% of ED visits in 2001 and 0.58% of ED visits in 2006 (Figure 2). Using our estimated frequency of allergic drug reactions, we then calculated the frequency of ED visits for patients with allergic drug reactions from 2007 to 2012 and found a continued rise, with an increase from 0.71% in 2007 to 0.94% in 2012.

DISCUSSION

The use of ICD-9-CM codes in epidemiologic studies of acute allergic reactions and anaphylaxis requires that these codes accurately and completely identify cases to ensure valid conclusions. Using a broad group of possible ICD-9-CM codes for drug allergy, along with E codes for ADRs, we identified 11,130 ED visits for possible allergic drug reaction between 2001 and 2006 and confirmed an allergic drug reaction in 27% of randomly sampled charts. Codes specific for drug reactions contained the largest percentage of allergic drug reactions, but using only these codes would have missed more than half of true drug allergy

cases. If only drug-specific codes had been used, more than half of the visits that involved drug reactions would have been missed, leading to a significant underestimation in the burden of drug allergy contributing to ED visits. Dual coding with a relevant *ICD-9-CM* code and E code was most accurate for identifying patients with allergic drug reactions; however, less than half of the patients with a confirmed allergic drug reaction had this dual coding. Most allergic drug reactions were attributed to antibiotics, intravenous contrast, and nonsteroidal anti-inflammatory drugs.

Using a combination of codes more accurately identifies patients with drug allergy; 76% of the patients coded with both a possible drug allergy *ICD-9-CM* code and an E code were found to have drug allergy, compared with patients with only an *ICD-9-CM* code (31%) or an E code (12%). However, this combination of codes would have identified only 50% of the visits by patients with allergic drug reactions and would have led to a significant underestimation of the incidence of drug allergy. In a study of patients presenting with acute urticaria, identified by *ICD-9* code, 20.7% were found to have drug reaction as the trigger.¹¹ Previous studies have shown that E codes have a high positive predictive value for ADRs but are not specific for allergic drug reactions.¹² Because only 10% to 15% of all ADRs account for unpredictable, dose-independent reactions that include drug hypersensitivity, finding that 12% of the visits with E codes are for drug allergy is consistent with previous studies.¹ A review of coding algorithms used to identify drug hypersensitivity reactions by *ICD-9* found that there is no specific *ICD-9* code that is accurate for identifying reactions and both specific and nonspecific codes must be used to obtain the true incidence of reaction.¹³ Using algorithms with combinations of codes may more accurately identify patients with allergic drug reactions than would any single code, but leads to an underestimate of the incidence of drug allergy.²⁻⁴ Validation of these algorithms is essential because only 75% of the patients with dual coding were found to have allergic drug reactions.

Consistent with many previous studies, antibiotics were the most common cause of allergic drug reactions in our study (42%), with penicillin the most frequent cause (34%).¹⁴⁻¹⁹ This was particularly striking in children, in whom antibiotics were responsible for 60% of the reactions and penicillin accounts for more than half of these reactions (55%).²⁰ In a Spanish study, beta-lactams were the most common culprit found on evaluation of an allergic drug reaction, accounting for 47% of the cases.²¹ A study using the National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance (NEISS-CADES) database implicated antibiotics in 19.3% of all ED visits for drug-related ADRs, with an estimated 142,000 ED visits each year attributable to antibiotic ADRs.²² Nearly 80% of these visits were due to allergic reactions, and penicillins and cephalosporins were implicated as the cause in half of these visits. Similar findings have been seen in pediatric inpatients, with antibiotics responsible for 33% of the ADRs.²³ This continues to support the necessity for good antibiotic stewardship. Minimizing unnecessary antibiotic use would decrease the risk of ADRs, particularly allergic drug reactions.

Overall, we found that the incidence of drug allergy in the ED is common and the rate is increasing. A recent study of drug-induced anaphylaxis estimated that there is 1 case of drug-induced anaphylaxis per 4000 ED visits.²⁴ Drugs accounted for 9% of the anaphylactic reactions in children seen in an urban

ED.²⁵ In our study, from 2001 to 2012, the estimated incidence for ED visits with allergic drug reactions rose from 0.49% to 0.94% of visits. This is higher than was seen in a 2004-2005 study looking at the incidence of ADRs using the NEISS-CADES database, in which ADRs were seen in 2.4 ED visits per 1000 population or 0.24% of ED visits, with drug allergies responsible for 33.5% of the reactions (0.08% of ED visits).²² A subsequent study of children using the NEISS-CADES database estimated the incidence for individuals 18 years or younger at 2 per 1000 or 0.20% of ED visits.²³ In a prospective study in Singapore in 2002, the estimated incidence of drug allergy was 4.2 cases per 1000 hospitalizations, which is similar to our estimate.¹⁹ The increased incidence of allergic drug reactions is consistent with an increased incidence in allergic reactions overall including reactions to foods and venom and anaphylaxis.

Further study of these codes in different settings is necessary to better understand the utility of diagnosis codes for epidemiology research on drug allergy. The present study was conducted in a single large, urban, teaching hospital and may not be generalizable to other settings (eg, rural hospitals). Because this study is a retrospective chart review, we are limited to the information recorded in the chart at the time of the visit and skin testing and the challenge could not be done to confirm allergy. In addition, this study is limited to patients treated in the ED, and it is important to validate the performance of the *ICD-9-CM* and E codes in other clinical settings (eg, inpatient ward and outpatient clinics). Using the *ICD-9-CM* codes recognized as having high utility in identifying cases of drug allergy from our data in the ED setting, we are currently reviewing inpatients who were billed with these codes, determining whether an allergic drug reaction was seen and the drug responsible. This will not only allow the *ICD-9-CM* codes that we have identified to be validated in the inpatient setting but also provide valuable information on the rate of drug allergy and the drugs involved. Validated *ICD-9-CM* codes will provide a valuable resource for the study of drug allergy using many large national data sets from the 1990s onward.

In summary, we have identified and validated by chart review *ICD-9-CM* and E codes that identify ED visits with allergic drug reactions. Allergic drug reactions can represent one-third of the ADRs, and these potentially life-threatening reactions are responsible for significant morbidity and costs. Understanding the clinical epidemiology of drug allergy is a crucial step in the management of these reactions and improving patient care when they occur.

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TABLE E1. Demographic characteristics for allergic drug reaction visits

Characteristic	Visits with allergic drug reactions (n = 444)	Visits without allergic drug reactions (n = 1190)	P value
Age (y), median (IQR)	43.6 (25.7-60.7)	39.5 (24.1-58.9)	.04
Sex: female, n (%)	248 (53)	624 (52)	.22
Race/ethnicity, n (%)			.76
White	316 (71)	833 (70)	
Black	28 (6)	95 (8)	
Hispanic	50 (11)	124 (10)	
Other/unknown	50 (11)	138 (12)	

IQR, Interquartile range.

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