

Utilization of hospital and outpatient care for adverse cutaneous reactions to medications

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SUMMARY

Purpose To quantify hospitalizations, visits to office based physicians, hospital clinics and emergency departments with primary diagnoses of skin conditions that are often due to drug reaction.

Methods I analyzed data from the National Hospital Discharge Summary (1997–2001), National Ambulatory Care Survey (1995–2000) and National Hospital Ambulatory Care Survey (1995–2000) to determine the number of hospitalizations and visits with primary diagnoses of skin conditions that are often attributed to drugs. Using statistical methods for surveys, I determined the demographic characteristics of patients with these diagnoses and compared them with patients seeking care for other reasons.

Results In the United States, there are about 5000 hospitalizations each year with a primary diagnosis of erythema multiform, Stevens–Johnson Syndrome or Toxic Epidermal Necrolysis, of which 35% are specifically ascribed to drugs. Annually, there are more than 100 000 outpatient visits for these diagnoses and about two million visits for immediate hypersensitivity reactions that may be due to drugs. Outpatient visits for drug eruptions and drug allergies that include a skin component exceed 500 000 annually.

Conclusions Skin conditions often attributed to drugs are frequent reasons for hospitalization and physician visits. Optimal care of the individual patients with these conditions requires careful attention to drugs as a possible cause. Copyright © 2005 John Wiley & Sons, Ltd.

KEY WORDS — drug eruption; Stevens–Johnson Syndrome; drug allergy; urticaria; hospitalization; epidemiology; federal survey; incidence

INTRODUCTION

Patients experiencing acute dermatologic conditions often attributed to drugs may seek care from office and hospital clinic based physicians. Particularly when more serious eruptions occur, care may be sought in emergency rooms and patients may be admitted to the hospital. Adverse cutaneous reactions to drugs often vary in severity, outcome and mortality.¹ These reactions are important because of both

of their direct effects and the loss of therapeutic benefit due to cessation of important medications possibly implicated in these reactions. A population based perspective of the frequency with which such adverse events occur, the characteristics of patients seeking care and the outcome of these events is lacking. To assess the type and frequency of medical care provided for dermatologic conditions often attributed to drugs, I utilized four national databases, which assess medical care utilization and include diagnostic and demographic information.^{2–4} I quantified the utilization of hospitalization, office visits, emergency rooms and hospital outpatient clinics for both more serious and less serious cutaneous diagnoses often due to drugs. I also assessed the demographic characteristics of patients who seek care for these diagnoses.

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Table 1. Diagnoses included in analysis by diagnostic group, ICD-9-CM code 5 and associated diagnostic terms

Diagnostic group	ICD-9CM codes	Diagnostic terms
SJS/TEN	695.1	Erythema multiforme, Stevens–Johnson syndrome, toxic epidermal necrolysis
Drug eruption	693.0	Dermatitis due to drugs (<i>excludes contact dermatitis</i>)
Drug allergy	995.2	Unspecified adverse effect of drug properly administered
Urticaria/angioedema	708.0	Urticaria, allergic urticaria, not otherwise specified, angioedema,
	708.9	angioneurotic shock edema, anaphylactic shock
	995.0	
	995.1	
	989.5	
Erythroderma	695.9	Erythroderma, exfoliative dermatitis
	695.89	
Adverse effect of drug properly administered	E 930 TO E 949	Adverse effect of drug properly administered* (<i>secondary diagnosis only</i>)

*Only considered in analysis of hospitalization data.

METHODS

Data sources

Each year the National Center for Health Statistics (NCHS) conducts national surveys, which quantify the utilization of health care services in the United States. These include the National Ambulatory Care Survey of office based care (NAMCS), the National Hospital Ambulatory Care Survey for Emergency Departments and Outpatients Departments (NHAMCS-ED) and (NHAMCS-OPD) and the National Hospital Discharge Survey (NHDS).² I used data from the NAMCS, NHAMCS-ED and NHAMCS-OPD for 1995–2000, the six most recent years available as of July 2003.^{3,4} For the NHDS, which samples about five times as many encounters each year as the other databases I analyzed data for 1997–2001 the five most recent years available as of July 2003. All four surveys include patient demographic information as well as diagnostic information for each sampled visit or hospitalization. All three surveys of ambulatory care (NAMCS, NHAMCS-ED, NHAMCS-OPD) also indicate whether a patient was admitted to the hospital and the patient's primary reason for the visit (i.e. why the patient said they were there). The NHAMCS-ED and NHDS record deaths, which are very rare in office and clinic practice and not recorded for the NHAMCS-OPD or NAMCS.

The NHDS records up to seven diagnostic codes International Classification of diseases, 9th Revision, Clinical Modification (ICD) for each admission.⁵ The ambulatory surveys record up to three diagnostic codes (ICD) for each visit.⁵ For all surveys, the first listed diagnosis is the principle diagnosis (reason) for the hospitalization or visit. To assess the number of visits

and admissions with specific dermatologic diagnoses that might be a result of a medication, I identified all sampled hospitalizations and visits with a primary ICD diagnostic code of a skin condition that is often due to a medication (Table 1).

As detailed in Table 1, I separately quantified the number of visits related to five broad diagnostic groups which include many of the acute dermatologic conditions often due to drugs: (1) SJS/TEN; (2) drug eruption (drug rash); (3) drug allergy; (4) allergic urticaria (including angioedema and anaphylaxis and (5) erythroderma. For hospitalization data, I also identified all admissions with a secondary (E-code) indicating a diagnosis of adverse event related to a therapeutic use of a drug properly administered (i.e. most often a drug induced eruption if the primary diagnosis is a cutaneous event) (see Table 1). To calculate rates of hospitalization or visits (per 1 000 000 person years) in the U.S. population, I used U.S. Census estimates for the U.S. Population by selected characteristic for 1 July 2000.

Data validation

The NHDS uses administrative data that are required by federal law and are the basis of reimbursement for Medicare and many other insurers. Medicare defines the primary discharge diagnosis as 'the main problem requiring in patient care'. There are specific rules for abstracting the medical record and determining 'the main problem. . .' and hence the diagnosis.

The ambulatory care databases, record both multiple diagnoses and patient's given reason for the visit.

I determined the proportion of outpatient visits with a primary diagnosis of ICD 695.1, who presented with

a patient complaint as the primary reason for the visit that was consistent with a sign or symptom of this diagnosis. To evaluate the likelihood of under ascertainment of EM/SJS/TEN in both databases, I identified records with a second diagnosis of ICD = 695.1 and examined the primary diagnoses for these cases. All four databases have been widely utilized as research and administrative data sources.

Statistical analysis

I estimated the total numbers of visits and admissions based on weights provided by the National Center of Health Statistics. I used STATA Release 8 survey procedures to calculate relative standard errors and 95% confidence intervals of these estimates and to test for the statistical significance of differences among groups.⁶

RESULTS

Data validation

Of 1 518 256 NHDS records assessed, 357 hospitalizations were identified with a primary diagnosis of ICD 695.1 and only 33 hospitalizations with this ICD as a second diagnosis. The first (primary) diagnoses for the 33 cases with a second ICD = 695.1 included a wide variety of reasons for admission, with the most frequent being HIV and cardiac disease.

A total of 474 465 ambulatory care records were assessed. A total of 42 had a primary diagnosis of ICD 965.1. This ICD was only one fourth as frequently recorded as a second diagnosis. For visits with a first diagnosis of ICD = 965.1 the patient's reason for the visit was skin rash or reaction to medicine, for 70% of visits with a first diagnosis of ICD 695.1. Only 12% of visits with this primary diagnosis had a reason for visit that was not a well recognized sign or symptom of a drug eruption.

Hospitalization

Based on sample weights, there were approximately 174 million admissions to acute care hospitals in the United States or about 35 million admissions per year. During this 5-year period, there were estimated 22 656 admissions with ICD primary (first) diagnosis 695.1 (EM/SJS/TEN) and an additional 14 701 admissions with this diagnosis listed as other than the first (primary) diagnosis. Of admissions for EM/SJS/TEN, 7930 (35%) were specifically coded as drug related. There were about five times more admissions (118 651) with urticaria/angioedema as a first diagno-

sis. However, only 14 583 (12%) of these admissions were specifically coded as 'allergic urticaria' (ICD = 708), and only 8243 (57%) admissions for 'allergic urticaria' were specifically coded as being a result of a drug (i.e. with relevant E code). Erythroderma was a far less frequent reason for admission (5029 admissions). A total of 29 346 patients were hospitalized with a primary diagnosis of drug eruption (not otherwise specified). Of these admissions, 25 768 (88%) were coded as drug related. Drug allergy was the primary diagnosis for 43 912 admissions and nearly all (92%) were also coded as drug related.

Table 2 compares the characteristics of patients admitted with a primary diagnosis of EM/SJS/TEN, drug eruption (not otherwise specified) and drug allergies with those patients hospitalized for all other reasons. Patients with a primary diagnosis of EM/SJS/TEN were younger than those admitted for all other reasons. Forty-three percent of EM/SJS/TEN patients were less than 16, six times the proportion of all hospitalizations for persons in this age group and more than four times the proportion of patients less than age 16 hospitalized for drug eruptions (Table 2). The percentage of all admissions with a primary diagnosis of drug allergy or drug eruption occurring in women (69%) was higher than the percentage for all hospitalizations (60%) $p < 0.001$.

The percentage of patients with a primary diagnosis of EM/SJS/TEN and a secondary E-code indicating a drug etiology did not vary greatly with age (age(s) 1–15 = 35%, ages 16–45 = 32%, age >45 = 37%). Among patients with a primary diagnosis other than those listed in Table 1, the percent with a secondary code indicating an adverse reaction to a drug properly administered was far lower (1.7%). For all primary diagnosis of skin conditions frequently related to drugs I assessed (see Table 1), deaths were less frequent (8/1000) than for all hospitalizations overall (23/1000 admissions). Death rates for persons admitted for EM/SJS/TEN were higher than overall death rates for persons admitted for other skin diagnoses that are often the result of drugs (Table 2). Among EM/SJS/TEN patients less than 65 years old, death was also infrequent (6/1000) but mortality rates were more than 10 fold higher (73/1000) among patients admitted with this diagnosis age 65 or older (odds ratio = 15.7, 95%CI = 2.3–108.8).

Overall, hospitalizations for skin conditions often related to drugs represented about 0.06% of all hospital admissions. Rates of hospitalization with a primary diagnosis of EM/SJS/TEN, Drug Eruptions and Drug Allergy were 16, 21 and 31 admissions per million person years respectively.

Table 2. Characteristics of patients hospitalized for EM/SJS/TEN, drug eruption, drug allergy and all other reasons, 1997–2001

ICD (code variable)	EM/SJS/TEN (695.1)	Diagnosis		
		Drug eruption (693.0)	Drug allergy (995.2)	Other diagnosis
Hospitalizations				174 000 000
N (95%CI)	22 656 (16 912–38 340)	29 346 (23 263–35 432)	43 912 (35 278–52 545)	
Age	29 ± 3* ^{†,‡}	51 ± 2* [†]	60 ± 2*	48
Age (years) (percent distribution)				
<20	48	8	7	19
20–64	35	50	47	45
>65	17	42	47	36
Male (%)	48 ± 4	28 ± 4*	33 ± 4*	40
Rate of admission	16	21	31	124
Length of hospital stay	5	3.5*	5	5
Died death rate [¶]	33	17	6*	23
HIV (%)	1.4	0.8	0.8	0.4
Drug induced (%)	35	88*	91*	1.7
White (%)	64	63	64	63

* $p < 0.05$ compared to other diagnoses.

[†] $p < 0.05$ compared to drug eruption.

[‡] $p < 0.05$ compared to drug allergy.

[§]Per million person years. (<http://www.census.gov/main/www/cen2000.html>)

[¶]Rate of death per 1000 admissions.

Ambulatory visits

From 1995 to 2000 there were 5.67 billion ambulatory visits to non-federal providers included in the three national surveys analyzed. More than 80 percent of ambulatory care (4.63 billion visits) was provided in an office-based setting, with the remainder nearly equally divided between emergency department (10%) and hospital clinics (8%). During these 6 years, there were a total of 650 000 visits with a primary diagnosis of EM, SJS, TEN, 1 million visits with a primary diagnosis of drug eruption, and nearly 6 million visits with a primary diagnosis of drug allergy

(Table 3). Of visits to office based practices and emergency room with a first diagnosis of drug allergy (ICD = 995.2), the patients reason for seeking care was a rash in about one fourth of cases and symptoms or complaints often associated with cutaneous allergic reactions such as mucus membrane complaints or fever in about one fifth of cases. Table 3 compares the characteristics of patients seeking outpatient care for these diagnosis and all other reasons. About half of patients with EM, SJS, TEN were under age 20, a substantially higher proportion than represented by this age group for other diagnoses (odds ratio = 4.0, 95%CI = 1.4–11.5) (Table 3).

Table 3. Number of visits (in 1000s) and characteristics of outpatients with a primary diagnosis of EM/SJS/TEN, drug eruptions, drug allergy and all other diagnoses (1995–2000)

ICDs	EM/SJS/TEN (695.1)	Diagnosis		
		Drug eruption (693.0)	Drug allergy (995.2)	Other diagnosis
Visits (1000s, 95%CI)	645 (310–990)	1005 (689–1321)	5835 (5023–6648)	5 670 000
Visits per year	110	170	970	9 450 000
Age (years) (percent distribution)				
<20	55	24	13	23
20–64	26	38	61	55
65+	20	38	26	22
Male (%)	29	26	33	41
Site of care distribution (percent)				
Office	82	80	68	82
Emergency department	12	13	27	10
Hospital outpatient	6	5	5	8
Admitted (percent)	0.7	0 (0%)	0.7	1.9

CARE FOR ADVERSE CUTANEOUS REACTIONS

Table 4. Number of visits (in 1000s) and characteristics of outpatients with a primary diagnosis of allergic urticaria, urticaria not otherwise specified and angioedema and anaphylaxis (1995–2000)

	Allergic urticaria	Diagnosis		
		Urticaria not otherwise specified	Angioedema and anaphylaxis	Total these diagnoses
ICDs	708.0	708.9	995.0, 995.1, 989.5	
Visits (1000s, 95%CI)	518 (372–664)	7013 (4389–9875)	4692 (3885–5500)	12 224 (10 900–13 500)
Visits per year (1000s)	86	1169	782	2037
Age (mean)	36	31	33	33
Age (years) (percent distribution)				
<20	33	35	23	34
20–64	50	55	55	55
65+	17	10	22	11
Male (%)	46	34	40	40
Site of care (percent) distribution				
Office	33	69	64	64
Emergency department	61	24	29	30
Hospital outpatient	6	7	6	8
Admitted to hospital (%)	0.9	0.5	0.8	0.7

Urticaria, angioedema, angioneurotic edema and anaphylactic shock related to any cause together account for three times as many outpatient visits as SJS/TEN/EM, drug rash and drug allergy combined. Table 4 presents the characteristic of outpatient visits for these diagnoses. Within the spectrum of anaphylaxis, angioedema and shock, only one diagnostic code is highly specific for being a drug reaction (ICD = 995.0 anaphylaxis due to a drug and Herxheimer's reaction). There were nearly 100 000 visits per year with this specific diagnostic code, but this code represented only 4% of all outpatient visits for the spectrum of reactions that includes urticaria of all types, angioedema and anaphylaxis of all types as detailed in Table 4. Outpatients with allergic urticaria were also highly likely to be treated in emergency rooms, but not very likely to be admitted to the hospital (Table 4).

Altogether, visits for the diagnosis detailed in Tables 3 and 4 that may be related to drugs account for less than 0.4% of all outpatient visits. However, together these diagnoses account for about 1% of all persons seen in emergency rooms.

DISCUSSION

Based on national databases, which sample large numbers of patients admitted to hospital or visiting physician's offices, emergency rooms and hospital outpatient clinics, I have assessed the rates of hospitalization and visits with a primary diagnosis of cutaneous eruptions that are often related to drugs. There are about 5000 hospitalizations per year with

the diagnosis of erythema multiforme, Stevens–Johnson Syndrome or TEN. For 35% of these reactions, a specific drug etiology was indicated. Assuming that only hospitalizations with a primary diagnosis in the spectrum of EM/SJS/TEN with a specific secondary diagnosis indicating a drug etiology account for all drug-related cases of SJS and TEN, I estimate that the rate of hospitalization for these drug-induced conditions at 6 per million persons per year in the United States. This rate is substantially higher than that calculated from enhanced reporting systems in Germany and France which principally ascertain hospitalizations for these conditions, but this estimate is consistent with the rate of hospitalization for drug related cases with this diagnosis in an HMO population.^{7–11}

The overall death rates of 3.3% for patients hospitalized with EM/SJS/TEN is substantially lower than that ascertained in referral based studies of this condition.^{7–9,12,13} This probably reflects the inclusion in the same ICD-code of the less serious diagnosis, EM, with the more often fatal SJS and TEN, which is also reflected in the high population of young patients with this diagnosis, who are most likely to have EM. As has been observed elsewhere in other studies, the death rates I observed increase with age.^{7–9,13,14} In my study, death rates were about ten times higher among individuals over 65 than younger persons. Death rates for patients admitted with a primary diagnosis of drug eruption or drug allergy were also lower than those observed for EM/SJS/TEN. Most admissions for drug allergy and drug eruption also had a secondary (E code) diagnosis indicating the condition was drug

induced. In contrast, only about one-third of EM, SJS and TEN cases were coded as being drug induced, significantly lower than the proportion in the largest case control studies of hospitalized patients.⁹ This finding is likely to reflect the inclusion of etiopathologically distinct conditions with the same diagnostic code (695.1).

Erythema multiforme is not usually drug related and most frequently occurs in younger persons. Stevens–Johnson Syndrome and toxic epidermal necrolysis are a spectrum of mucocutaneous bullous disorders that are usually drug induced and are clinically distinct from erythema multiforme.¹⁵ Clearly, improved classification systems that provide separate codes for conditions that are clinically and etiologically distinct will improve the utility of such systems. Average length of stay for all patients admitted for drug allergy and EM, SJS and TEN was comparable to that for other hospitalized patients. There was a trend for patients with drug-related skin diseases to be more often also diagnosed as having HIV infection. Because of small numbers, this did not reach statistical significance. Patients admitted for drug allergy and drug eruptions were older than patients admitted for all other diagnoses and than patients admitted for EM, SJS and TEN. When only persons over the age 20 are considered, the mean age of persons admitted for EM/SJS/TEN and those admitted for all other causes are similar (52 vs. 58 years).

Taken together, EM, SJS, TEN, drug eruptions and drug allergy account for about 65 hospitalizations per million person-years in the United States, or about 1 in 2000 admissions to U.S. acute care hospitals. However, many and perhaps a majority of hospitalizations with a diagnosis of drug allergy may have not had skin findings. Roughly 100 000 hospital days per year are devoted to the care of patients with these conditions, suggesting that total expenditures for hospital care of these conditions is likely to exceed 100 million dollars per year.

Outpatient visits with primary diagnosis of drug allergy were nearly ten times more common than those for drug eruption and EM/SJS/TEN combined and total about 1 million visits per year. In about one fourth of cases, the patient's primary complaint included symptoms of a rash. For an additional one fifth of patients with a diagnosis of drug allergy presenting complaint was a sign or symptom also often associated with a drug eruption. Even more common are visits for urticaria and angioedema which total more than 2 million visits annually. However, only about 5% of these visits were classified as allergic urticaria. Nondrug etiologies are likely to account for a substantial majority of cases of angioedema and

urticaria, but excluding a drug etiology is essential for all cases lacking a clear alternative etiology.¹⁶

Outpatient visits given a primary diagnosis of EM/SJS/TEN are about 20-fold more frequent than hospitalizations for other diagnoses, totaling more than 100 000 per year. Drug allergies in particular are often cared for in the emergency room (27% of visits, vs. 10% of all outpatient care). As observed for inpatients with ICD 695.1 (EM/SJS/TEN), the average age of out patients with this diagnosis is significantly lower, than that for patients seeking care for drug allergy and drug eruption. This probably reflects the large number of young persons seeking care for EM related to factors other than drugs. Among those over 35, the average age of persons seeking care for EM/SJS/TEN was comparable to that of patients seeking care for all other diagnoses. Females were significantly more likely to seek care for EM/SJS/TEN, drug eruptions and drug allergy than were men.

Although the odds of utilizing the emergency room for outpatient care for drug allergy and eruptions are six times higher than that of all other outpatient diagnoses, the rate of hospitalizations among persons seeking outpatient care for these diagnoses is significantly lower (about half), than that of all other outpatient visits. Patients seeking care for urticaria, anaphylaxis and angioedema in emergency rooms were only one-twentieth as likely to be admitted to the hospital as other emergency room patients. This finding is consistent with the acute but when properly treated self-limited nature of these reactions.

Hospitalization for drug allergy, EM/SJS/TEN and drug eruptions account for about 1 in 2000 hospitalizations, about one-tenth the number of cases determined in a prospective study in a single institution in France.¹⁷ However, I included only cases whose principal reason for admission was a potential drug-related event. In contrast, the French study included cutaneous drug reactions that developed in the hospital, were incidental findings, and were not necessarily the principle reason for the admission. My sample is representative of all hospitals, whereas the French study included only an academic health center, which may also explain the differences. For example the prevalence of HIV infection among individuals with cutaneous drug reactions in that academic health center were about ten times that of HIV for all persons in my study.¹⁷

Strengths and limitations

The databases I analyzed have been widely utilized in medical research. More than 500 peer reviewed

articles have utilized these data including ones published in leading journals such as the *New England Journal of Medicine*.^{18,19}

For ambulatory care data, the physician's primary diagnosis was collected along with the patient's stated reason for the visit an assessment of the likely compatibility between diagnosis and presenting complaint. Most patients with a first diagnosis of EM/SJS/TEN had sought care for a skin problem and this diagnosis as a secondary diagnosis in the database was infrequent. However, as is the case in any study based on clinician's diagnosis and not based on pre-determined criteria, the accuracy of the diagnosis depends on the clinician's diagnostic abilities.

Prior studies of a Medicaid claims database suggest that when a record is available for expert review, the experts frequently disagree with the discharge diagnosis of EM/SJS/TEN (ICD.695.1).¹¹ This finding of this study that about one-third of hospitalizations with ICD 695.1 is considered by the treating physician to be an adverse reaction due to a drug is consistent with these expert findings.¹¹

Although my study is broadly representative and uses the same methods to determine health care utilization for specific diagnoses as benchmark studies of other diagnoses, studies of this type have limitations.^{18,19} For example these data cannot determine the proportion of these cutaneous events that were the result of re-administration of a drug to which a patient had a prior reaction and should be avoidable versus the first-time occurrence of cutaneous drug reactions that could not have been predicted. However, the large number of visits for drug allergies with a cutaneous component and drug eruptions and allergic urticaria are consistent with the reported high prevalence of one or more drug allergies in a surgical population. These data represent individual clinician's diagnoses and are subject to diagnostic error. However, there are about 2 500 000 visits each year for the spectrum of conditions we studied, with skin and mucus membrane findings. Many of these cases are drug induced. The high frequency of such visits support the importance of physicians' understanding of the possible role of drugs in these reactions and their being attentive to and expert in their treatment. Although, the available data do not permit a precise estimate of the proportion of these visits that represent skin conditions, which were due to drugs, clinicians should consider medications as a possible cause for all patients presenting with the clinical features of the diagnoses listed in Table 1, particularly when an alternative etiology is not readily apparent. A complete drug history, including information of the timing of the administration of each drug

KEY POINTS

- Hospitalization for erythema multiforme, Stevens–Johnson Syndrome, drug eruptions and drug allergy are frequent.
- Urticaria and angioedema are often seen in the emergency room and physicians' offices but are seldom a reason for hospitalization.

relative to the onset of the eruptions, as well as the use of nonprescription drugs and homeopathic therapies, is essential.

Unfortunately, to date unbiased data that pinpoint the relative and absolute risks of most of these reactions in association with specific drugs are largely lacking.

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