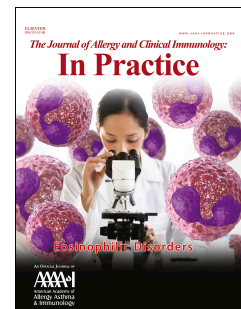


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Reporting of Drug Reaction with Eosinophilia and Systemic Symptoms from 2002-2019
in the FDA Adverse Event Reporting System (FAERS)

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Key words: Drug Reaction with Eosinophilia and Systemic Symptoms; DRESS; FDA Adverse Event Reporting System; FAERS

Clinical implications: Of drug reaction with eosinophilia and systemic symptoms (DRESS) cases identified in the FDA Adverse Event Reporting System (FAERS), 5 drugs account for >50% of cases, and 3 have actionable HLA risk factors identifying implementation strategies for prevention and earlier diagnosis.

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a drug-induced severe cutaneous adverse reaction that is often overlooked due to its overlap with other infectious and inflammatory illnesses; however, early identification and treatment are key in preventing associated morbidity and mortality^{1,2}. Historically, anticonvulsant use in association with DRESS syndrome was cited as early as the 1930s with initial descriptions involving drug-associated hypersensitivity². In the 1950s, the term drug-induced pseudolymphoma described syndromes of cutaneous symptoms with organ involvement and other systemic features. Ultimately, in the 1990s, DRESS was designated to describe patients with specific hematological and organ abnormalities and lymphadenopathy that was typically associated with an extensive rash, findings on histopathology, and delayed time to recovery³.

Today, the most common causal drugs of DRESS include antibiotics and aromatic anticonvulsants, but due to the delayed onset of symptoms that typically occurs a minimum of 2 weeks after drug initiation, the implicated drug may be overlooked, and the incidence is likely

underreported. Studies have reported the incidence or risk of DRESS to range from 1 in 1,000 to 1 in 10,000 drug exposures^{1,2}. However, despite a relatively low incidence, the associated morbidity and mortality, including high health care costs and death in up to 10% of patients, raise the importance of prevention and early treatment of this patient population¹. Variation in class I HLA has recently been shown to be a prominent risk factor for DRESS, although the specific class I HLA associated with a specific drug in a specific population is largely unknown for most drugs. In particular, HLA class I alleles have been associated with multiple drug-specific severe T-cell mediated drug reactions and may help lead to prevention screening strategies or early recognition and drug discontinuation in at risk populations⁴. To gain insights into the epidemiology of reported DRESS cases, we reviewed the FDA Adverse Event Reporting System (FAERS) database to determine which drugs are most frequently reported to FAERS in association with DRESS and fatal DRESS.

The publicly available FAERS database was searched from 2002-2019 using the term “drug reaction with eosinophilia and systemic symptoms.” FAERS is a database where drug manufacturers report drug associated adverse events but reports can also be voluntarily initiated by patients or healthcare providers. The data collected and reported in the FAERS database includes patient demographics such as age and sex but not race. In addition, a detailed problem list including presence or extent of organ involvement which may play a role in a patients’ outcome is not a reporting requirement. Although FAERS and other similar databases come with limitations including significant reporting bias, they still contain a large collection of drug-associated adverse events. To determine the DRESS reaction date, FAERS’ “Earliest FDA Received Date” was selected rather than “Latest FDA Received Date” as a better representation of when the DRESS reaction occurred. The top 5 drugs associated with DRESS were determined

for the 5 countries reporting the most FAERS DRESS cases: France, United States, Japan, United Kingdom, and Spain. Annual trends were evaluated as a percent of total DRESS cases over time and total fatal DRESS cases both overall and by each of the top 5 drugs.

We also reviewed the FAERS database from 2002-2019 for reports using the term “drug reaction with eosinophilia and systemic symptoms” that resulted in death. Using previously reported methods, we sorted reports by generic drug names, reaction date, country, sex, age, and whether their outcome was death⁵.

From 2002-2019, 0.09% (15,324/16,887,214) of FAERS adverse drug events were reported as DRESS, with no DRESS reports before 2002 which is likely accounted for by a change in nomenclature. For instance, in the 5 years prior to 2002, the most common allopurinol associated cutaneous reaction in FAERS was dermatitis (17.8%) which in 2002-2019 changed to DRESS (33.7%). The median age of patients at time of DRESS was 51 years [IQR: 34] and 52.03% were female. The median age in fatal cases was 61 years but varied significantly between drugs. FDA-reported DRESS reactions and fatal DRESS reactions to all agents both increased sharply through our study period, but the percentage of reported DRESS reactions that were fatal decreased from 14% in 2003 (3 deaths in 21 cases) to 5.2% in 2019 (120 deaths in 2319 cases). (**Table 1**). Since FAERS does not require reporting of comorbidities nor specific manifestations of DRESS, determinants of morbidity and mortality cannot be reliably ascertained from this database. Interestingly, 422 of DRESS reports also had "Stevens-Johnson syndrome," "SJS-TEN overlap," or "toxic epidermal necrolysis" listed as their reaction, and those cases were more likely to be fatal (28.0% overall compared to 6.9% of DRESS cases alone with allopurinol, vancomycin, & trimethoprim-sulfamethoxazole having the highest fatalities).

The top 5 drugs associated with DRESS were allopurinol, vancomycin, lamotrigine, carbamazepine, and trimethoprim-sulfamethoxazole, accounting for 46.8% (7,164/15,324) of reported cases and 51.9% (550/1,059) of reported deaths. Interestingly, of the top 10 drugs that had 500 or more associated DRESS events reported to the FDA, only allopurinol does not fall into the categories of either an antiepileptic or antimicrobial drug. There were significantly more females affected by lamotrigine DRESS (68%), $p<0.001$ and fatal DRESS (63%), $p<0.001$. The median age for lamotrigine DRESS (37 years [IQR: 30]) and fatal DRESS (32 years [IQR: 30]) were significantly younger than the overall median of 51 years ($p<0.001$). Although DRESS reactions to trimethoprim-sulfamethoxazole were predominantly male (54.72%, $p<0.001$), more females than males were reported to have fatal trimethoprim-sulfamethoxazole DRESS reactions, 60% ($n=39/65$, $p<0.001$) (**Online Table E1**). In explaining the slight male representation for reported trimethoprim-sulfamethoxazole DRESS, 91 out of the 908 trimethoprim-sulfamethoxazole FAERS DRESS reports mentioned "HIV" or "opportunistic infection prophylaxis" in their reason for use. Out of these, 81.0% were male, compared to 54.7% of all trimethoprim-sulfamethoxazole DRESS reports and 51.3% of trimethoprim-sulfamethoxazole reports without listing HIV or opportunistic infection prophylaxis as reasons for use. The 5 countries with the most DRESS reports in FAERS were France, the United States, Japan, the United Kingdom, and Spain. France was listed for 29.25% of all DRESS reports in FAERS, while the next highest was the United States at 17.76%. When the top 5 DRESS-related drugs are stratified by country, France was the top contributor to reports of allopurinol, vancomycin, and trimethoprim-sulfamethoxazole DRESS, and Japan was the top contributor to reports of lamotrigine and carbamazepine DRESS. There were no antiepileptic drugs in France's

top 5 DRESS-related drugs and no antibiotics in Japan's. Of the top 5 drugs, allopurinol was the only one represented in the top 5 drugs of each of the top 5 countries (**Table 1**).

Our review of the FAERS database defined several important aspects of the epidemiology of DRESS. Currently, 5 drugs (carbamazepine, lamotrigine, vancomycin, trimethoprim-sulfamethoxazole and allopurinol) account for almost half (46.8%) of DRESS cases from FAERS reports globally. Reactions to the top 5 drugs also account for the majority of DRESS associated deaths; although, fatalities have decreased over time (**Figure 1**). The decreasing trend may reflect better diagnosis or management of DRESS that is not captured by the FAERS database. Drugs accounting for over one-third of reported DRESS associated deaths (39.4%) notably have actionable HLA risk factors such as vancomycin (HLA A*32:01), carbamazepine (HLA A*31:01), and allopurinol (HLA B*58:01)⁶⁻⁸. These three drugs show considerable variability in their reporting frequency globally which in the case of vancomycin appears proportionate to the frequency of known HLA-A*32:01 representation in these populations (Online **Figure E1**). Although countries differ in reporting requirements for adverse drug reactions (ADRs) and this may impact the overall proportion of countries represented in FAERS (e.g. in France reporting to pharmacovigilance databases is a legal requirement), this should not necessarily impact the distribution of drugs reported for a given country.

In conclusion, the top drugs associated with DRESS in the FAERS system have known potentially actionable HLA risk factors and geographic disparities in reporting, which further highlights the need for heightened vigilance to improve preventive efforts, increase awareness, and promote early diagnosis and treatment of DRESS.

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Figure legend:

Figure 1

A) The total number of DRESS cases reported to the FDA Adverse Event Reporting Systems (FAERS) annually from 2002-2019.

B) The percentage of DRESS cases reported to FAERS annually from 2002-2019 in association with each of the top 5 drugs (allopurinol, vancomycin, lamotrigine, carbamazepine, trimethoprim-sulfamethoxazole).

C) The total number of fatal DRESS cases reported to the FDA Adverse Event Reporting Systems (FAERS) annually from 2002-2019.

D) The percentage of fatal DRESS cases reported to FAERS annually from 2002-2019.

Table 1: Top 5 Drugs Associated with a Report of DRESS to FAERS from 2002–2019 and top reporting countries					
All Drugs		Allopurinol		Vancomycin	
Country Name	DRESS Cases (% of Cases with Associated Country)	Country Name	DRESS Cases (% of Cases with Associated Country)	Country Name	DRESS Cases (% of Cases with Associated Country)
Total Cases	15324	Total Cases	2255	Total Cases	1625
Cases with Associated Country	13099	Cases with Associated Country	1768	Cases with Associated Country	1447
France	3832 (29.25%)	France	403 (22.79%)	France	495 (34.21%)
United States	2327 (17.76%)	United States	168 (9.5%)	United States	476 (32.9%)
Japan	1359 (10.37%)	Portugal	140 (7.92%)	United Kingdom	74 (5.11%)
United Kingdom	592 (4.52%)	South Korea	109 (6.17%)	Canada	50 (3.46%)
Spain	578 (4.41%)	Thailand	107 (6.05%)	Switzerland	48 (3.32%)
Portugal	337 (2.57%)	Spain	96 (5.43%)	Australia	42 (2.9%)
South Korea	334 (2.55%)	Taiwan	85 (4.81%)	Japan	40 (2.76%)
Italy	306 (2.34%)	China	83 (4.69%)	Netherlands	31 (2.14%)
Switzerland	243 (1.86%)	Japan	82 (4.64%)	Spain	27 (1.87%)
Canada	236 (1.8%)	Italy	81 (4.58%)	Portugal	22 (1.52%)
Lamotrigine		Carbamazepine		Trimethoprim-sulfamethoxazole	
Country Name	DRESS Cases (% of Cases with Associated Country)	Country Name	DRESS Cases (% of Cases with Associated Country)	Country Name	DRESS Cases (% of Cases with Associated Country)
Total Cases	1590	Total Cases	1080	Total Cases	908
Cases with Associated Country	1413	Cases with Associated Country	800	Cases with Associated Country	821
Japan	396 (28.03%)	Japan	277 (34.63%)	France	380 (46.29%)
France	286 (20.24%)	France	162 (20.25%)	United States	163 (19.85%)
United States	267 (18.9%)	United States	46 (5.75%)	Japan	62 (7.55%)
United Kingdom	58 (4.1%)	United Kingdom	40 (5%)	United Kingdom	33 (4.02%)

Spain	40 (2.83%)	Poland	34 (4.25%)	Spain	33 (4.02%)
Turkey	36 (2.55%)	Tunisia	26 (3.25%)	Singapore	23 (2.8%)
Mexico	24 (1.7%)	Spain	25 (3.13%)	Australia	19 (2.31%)
Canada	23 (1.63%)	Portugal	22 (2.75%)	Switzerland	17 (2.07%)
India	23 (1.63%)	Turkey	16 (2%)	Netherlands	16 (1.95%)
China	23 (1.63%)	Italy, India, Taiwan, Mexico	13 (1.63%)	Hong Kong	10 (1.22%)

Table e1: The Top 5 Drugs Associated with a Report of DRESS to the FDA from 2002-2019

Drug Name and Rank	Total Adverse Event Reports	DRESS (% of Total Adverse Event Reports) Bolded if >10%	United States DRESS (% of Drug- Specific DRESS Cases)†	Maximum DRESS Cases in a Year (Year)	Reported Female (%) (n=42816)†	Median Age [IQR] (n=35727)†	Average % Change per Year (95% CI)*
Overall Database from 1999-2019	16887214	15324 (0.09%)	2327 (15.19%)	2319 (2019)	7218 (52.03%)	51 [34]	144 (122, 167), P < .001
Top 5 Drugs Combined	143520	7164 (4.99%)	1099 (15.34%)	1119 (2019)	3338 (50.81%)	53 [33]	
1. Allopurinol	14158	2255 (15.93%)	168 (7.45%)	365 (2019)	958 (46.96%)	65 [24]	0.60 (0.32, 0.89), P < .001
2. Vancomycin	22992	1625 (7.07%)	476 (29.29%)	310 (2019)	665 (44.72%)	55 [27.5]	1.06 (0.14, 1.99), P = .03
3. Lamotrigine	53986	1590 (2.95%)	267 (16.79%)	234 (2018)	1001 (68.05%)	37 [30]	0.71 (0.12, 1.30), P = .02
4. Carbamazepine	28300	1080 (3.82%)	46 (4.26%)	124 (2018)	483 (48.59%)	44 [36]	-0.46 (-0.84, 0.02), P = .06
5. Sulfamethoxazole - Trimethoprim	27894	908 (3.26%)	163 (17.95%)	194 (2019)	379 (45.28%)	54.5 [35]	1.76 (1.04, 2.48), P < .001

† Cases without country, sex, or age data (depending on the specific measurement) were excluded from these denominators for each drug and drug class.

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Figure legend:**Figure e1:**

Risk allele carriage frequency of HLA A*32:01 by each of the top 5 countries reporting DRESS compared to the rate of reported vancomycin-specific DRESS for each country showing drug-specific DRESS may be proportionate to the frequency of known associated HLA allele carriage in each population

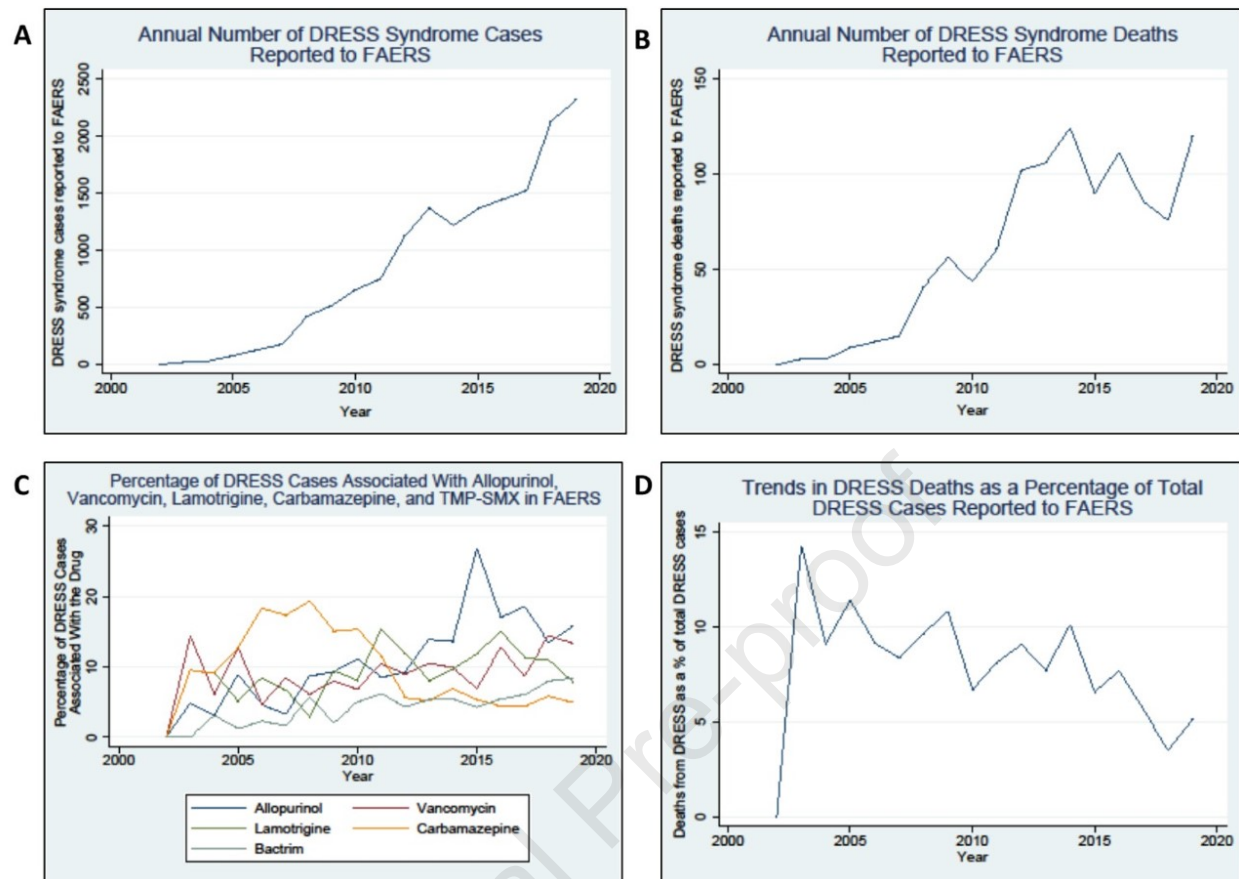


Figure e1

HLA A*32:01 vs. Vancomycin DRESS frequency by country

