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# Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Identified in the Electronic Health Record Allergy Module

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## Abstract

**Background:** Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a rare but severe hypersensitivity reaction that remains poorly characterized in the US.

**Objective:** We aimed to identify and describe DRESS syndrome cases in an integrated healthcare system using electronic health record (EHR) allergy module free text searches.

**Methods:** We identified DRESS syndrome cases with rash, absolute eosinophil count ≥500/L, organ involvement, and RegiSCAR (European Registry of Severe Cutaneous Adverse Reactions [SCAR]) to Drugs and Collection of Biological Samples) score ≥2 by reviewing patients from

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ARW, KGB and LZ designed the study.
ARW, OAC, NAP performed data abstraction.
ARW, KGB and YL performed data analysis.
ARW, KGB and YL analyzed and interpreted the results.
ARW drafted the first report.
ARW, KGB, YL, LZ, OAC, NAP assisted with interpretation and revision of the report.
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NAP discloses spousal employment by Chiesi Farmaceutici; this is unrelated to the submitted manuscript.
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1980–2016 whose EHR allergic reaction matched DRESS-related keywords. Liver injury required alanine aminotransferase ≥100U/L and renal injury required creatinine increase by ≥0.5mg/dL or 50%. Patient and DRESS characteristics were described, resource use was determined, and cost was estimated.

**Results:** Among 3,162,562 patients with 3,319,387 million allergy entries, 538 reactions matched keywords, and 69 were DRESS cases (prevalence 2.18 per 100,000). DRESS patients had liver (42%) or renal (42%) injury; 11 (16%) had both liver and renal injury. Primary drug culprits were antibiotics (74%) (vancomycin [39%], beta-lactams [23%], fluoroquinolones [4%], tetracyclines [4%], and sulfonamides [3%]) and anticonvulsants (20%). Of 65(94%) hospitalized DRESS patients, 43 (66%) were hospitalized for DRESS syndrome management with median length of stay 9 days [IQR, 6–17 days] and cost approximately $17,101 per patient.

**Conclusions:** Using free text search of the EHR allergy module identified a large US DRESS syndrome cohort. DRESS prevalence was 2.18 per 100,000 patients. Both liver and kidney injury were frequent, and vancomycin was the most common drug culprit. DRESS cases were morbid and resource-intensive.

### Keywords

Drug-induced hypersensitivity syndrome; Anticonvulsant hypersensitivity syndrome; Severe cutaneous adverse reaction; Hypersensitivity; Resource; Cost

## INTRODUCTION

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome was first recognized as a cutaneous reaction to sulfanilamide in 1937[1] and as a pseudo-lymphoma reaction to anticonvulsants in 1959.[2] While still commonly referred to as Anticonvulsant Hypersensitivity Syndrome (AHS),[3] the hypersensitivity reaction (HSR) is now largely recognized as DRESS syndrome, and many other causative drugs and drug classes, including antibiotics, allopurinol, and non-steroidal anti-inflammatory drugs have since been implicated.[4–7]

The clinical presentation of DRESS syndrome includes rash, fever, eosinophilia (absolute eosinophil count [AEC] ≥500/L), and organ injury (typically liver and/or kidney, but other organs such as the lung, heart, gastrointestinal tract, or others can be involved).[8,9] DRESS syndrome may present days to weeks into a medication course, and can even present after medication discontinuation.[4,5,8–10] DRESS syndrome causes substantial patient morbidity and carries a mortality of 5–10%.[3–5,9,11] The cornerstone of DRESS syndrome treatment involves the identification and withdrawal of the culprit drug. While corticosteroids are commonly used for DRESS syndrome treatment, their efficacy has not been established.[12]

Our current understanding of DRESS syndrome is largely based on international data from Asian and European registries.[4–6,8–11] US based data have come from case reports and series.[11] While International Classification of Diseases ninth/tenth edition (ICD-9/10) billing codes can be used to study severe cutaneous adverse reactions (SCARs) and general HSRs, [13] no specific codes exist for DRESS syndrome. Given the recent expansion of EHRs in US healthcare systems [14,15] and Meaningful Use standards requiring EHRs to maintain active

allergy lists,[16,17] we aimed to identify and describe DRESS syndrome cases using free-text search of the EHR allergy module in a large integrated US healthcare system.

## METHODS

### Study Design and Population Identification

This retrospective study identified potential DRESS syndrome cases at Partners HealthCare System (PHS), Boston, MA, using allergy records in the EHR allergy module from 1980 through October 2016. Of note, in the 1980s and 1990s, not all PHS providers used the EHR. Since DRESS syndrome does not exist as a coded reaction field in the EHR, to identify cases, we searched free text within the allergen name, allergy reactions, and comments fields,[18] using an allergist-defined list of DRESS-related keywords: Eosinophilia, hypersensitivity syndrome, DRESS, drug-induced hypersensitivity syndrome, Anticonvulsant Hypersensitivity Syndrome (AHS), and drug hypersensitivity syndrome.

The EHR was reviewed for all possible DRESS cases by medical doctors trained in diagnosing and managing drug HSRs (authors ARW, OAC, NAP). Patient data included demographic details (e.g., age, sex), specific patient comorbidities at the time of the DRESS diagnosis (e.g., hypertension, seizures), and reaction details (e.g., culprit drug, rash morphology, laboratory results, treatment administered). All data were collected and maintained using Research Electronic Data Capture (REDCap) tools hosted at PHS.[19]

### DRESS Syndrome Criteria

DRESS syndrome patients had to have a rash, eosinophilia (AEC ≥500/L),[20] and organ injury. We adapted organ injury criteria from prior studies, including RegiSCAR, and defined liver injury as alanine aminotransferase (ALT) ≥100U/L and kidney injury as at least 0.5mg/dL or 50% increase above baseline creatinine.[21,22,23] Because patients did not have a RegiSCAR[23] score calculated at the time of the HSR, and retrospective EHR data contained unknown RegiSCAR fields, we used a modified RegiSCAR score that excluded “resolution in greater than 15 days.” A modified RegiSCAR score ≥2, and a clinical presentation diagnosed as DRESS syndrome by the patients’ clinicians, was also required to meet the DRESS syndrome case definition in this study.

To determine causative drug, we used clinical assessments in notes and the allergy module at the time of the HSR. For patients who had multiple drugs considered possible HSR culprits, we included only the primary drug thought responsible by the treating clinicians. When no opinion was given regarding the primary culprit drug, the most likely culprit drug was determined retrospectively from available data.

For DRESS patients who were hospitalized, we used patients’ primary discharge diagnosis to determine if the admission was for DRESS syndrome (i.e., chief complaint of “DRESS syndrome” or similar [e.g., “drug reaction”]) [23] or whether DRESS was a complication of an existing hospitalization.

### Healthcare Resource Utilization and Cost

We recorded hospital length of stay, including any intensive care unit (ICU) time and type, and the number of specialty consultant physician teams involved in the care of DRESS patients. To estimate the cost of DRESS syndrome for hospitalized patients, we first determined the total direct cost of an average stay on an inpatient floor and ICU for hospitals within PHS. This cost included: Relative value units; fixed costs, such as salaries of operational staff and costs of non-capital equipment; and variable expenses, such as gloves, dressings, equipment; and nursing costs. We used the median total direct costs per day per unit and length of stay per unit, along with the professional costs associated with consultations using relative value unit costing methodology and assuming one new consultation (billing code 99223) and three subsequent hospital care visits (billing code 99233). The cost for patients hospitalized specifically for DRESS syndrome, therefore, approximates the cost of US DRESS syndrome cases that require hospitalization in 2016 US dollars.

### Statistical Analyses

We divided DRESS syndrome patients into three groups for clinical comparisons: Those with liver injury alone, those with kidney injury alone, and those with both liver and kidney injury. Descriptive data were displayed as numbers, frequencies, and medians with inter-quartile ranges (IQR). Categorical variables were compared using Fisher's exact test. For continuous variables, we used the Wilcoxon Rank Sum test for comparisons of 2 groups and Kruskal-Wallis Test for multi-group comparisons. Statistical analyses were performed in SAS version 9.4 (Cary, NC, USA). This study was approved by the Partners Institutional Review Board.

## RESULTS

### DRESS Syndrome Epidemiology and Case Identification

Between 1980 and 2016, there were 3.2 million patients with 3.3 million allergy entries stored in our EHR data repository. From the keyword search, we identified 538 HSRs; 69 patients (2.18 in 100,000 patients) had DRESS syndrome. DRESS syndrome involved liver injury (58%) and renal injury (58%). Twenty-nine (42%) had liver injury alone, 29 (42%) had kidney injury alone, and 11 (16%) had both liver and kidney injury (Figure 1).

### DRESS Syndrome Patient Characteristics

Patients with DRESS had median age 60 years and were 55% female (Table 1). Common comorbid conditions included hypertension (55%), seizures (19%), diabetes mellitus (17%), and coronary artery disease (13%). There were 31 (45%) patients with less than or equal to 1 specified comorbidity, 29 (42%) with 2–3 specified comorbidities, and 9 (13%) with ≥4 specified comorbidities.

### DRESS Syndrome Clinical Presentation

For 38 (55%) of the patients, their HSR was attributed to 1 drug (Table 2). DRESS syndrome was similarly attributed to only one drug across subgroups of DRESS patients,

including those with liver injury only (59%), kidney injury only (52%), and both liver and kidney injury (55%, p>0.5). Thirty-one patients (45%) had 2 or more implicated drugs.

Vancomycin (n=27, 39%) was the most common culprit causing DRESS syndrome. A greater percentage of patients in the subgroup of DRESS with kidney injury only had vancomycin as the drug culprit as compared with patients in liver injury only subgroup or both liver and kidney injury subgroup (55% vs 24% and 36%, p=0.06). Fourteen patients (20%) experienced DRESS syndrome attributed to an anticonvulsant: 6 (21%) of the patients with liver injury, 4 (36%) of the patients with liver and kidney injury, and 4 (14%) with kidney injury. However, the frequency of DRESS attributable to anticonvulsants was not different between these subgroups (p = 0.31). Sixteen (23%) patients had DRESS syndrome due to beta-lactams. Six (21%) patients in the cohort of DRESS patients with kidney injury had their DRESS attributed to a beta-lactam, whereas 8 (29%) patients in the liver injury cohort and 2 (18%) in the kidney and liver injury cohort had DRESS attributed to beta-lactams (p>0.5).

Using the RegiSCAR criteria, 40 (58%) patients were categorized as “possible DRESS,” 27 (39%) patients had “probable DRESS,” and 2 (3%) pat ients had “definite DRESS.”

The most common rashes were described as maculopapular (n= 55, 80%). Maculopapular rash was observed in DRESS with liver injury 86% of the time compared to DRESS with kidney injury 72% of the time, and was seen in 82% of the cases of DRESS with both kidney and liver injury (p=0.48). Erythema was also common with 40 (58%) of DRESS patients experiencing erythema, without a differential pattern between DRESS cohort subgroups (p=0.23).

DRESS patients had median AEC 1,850/L [IQR, 890/L-3,390/L], with AEC levels comparable between subgroups.

In the liver injury only subgroup, the median maximum ALT was 226U/L [IQR, 178U/L-457U/L] and median change in ALT was 196U/L [IQR, 159U/L-391U/L]. In the subgroup with both liver and kidney injury, the median maximum ALT was similar: 234U/L [IQR, 142U/L-458U/L] and a median change in ALT of 185U/L [IQR, 114U/L-423U/L].

In the kidney injury subgroup, the median maximum creatinine was 2.63mg/dL [IQR, 1.87mg/dL-4.72mg/dL], and the median change in creatinine was 1.44mg/dL [IQR, 0.91mg/dL-3.68mg/dL]. In the subgroup with both liver and kidney injury, the median maximum creatinine was similar: 2.29mg/dL [IQR, 1.74mg/d-4.89mg/dL], and the median change in creatinine was 1.08mg/dL [IQR, 0.90mg/dL-1.20mg/dL].

Use of any corticosteroid was part of treatment for 51 (74%) DRESS syndrome patients, with no observed differential use between organ injury subgroups (p>0.5). Thirty-five (51%) DRESS patients received topical steroids, 36 (52%) received oral steroids, and 26 (38%) received intravenous steroids. Parenteral steroids were used more frequently in DRESS patients with both liver and kidney injury (45%), and in patients with kidney injury alone (48%) compared to liver injury alone (24%, p=0.17).

### DRESS Morbidity, Mortality, and Resource Use

Sixty-five (94%) DRESS syndrome patients were hospitalized (Table 3). Of these, 43 (66%) were hospitalized for DRESS syndrome diagnosis and treatment while 22 (34%) were hospitalized for other reasons when they developed DRESS syndrome.

Patients hospitalized had median length of stay of 15 days [IQR, 7 days-30 days]. Median length of stay for patients hospitalized for DRESS syndrome alone was shorter than for patients with DRESS who were hospitalized for other reasons (9 days [IQR, 6 days-17 days] vs 36 days [IQR, 19 days-43 days], $p<0.001$). Twenty-three (35%) DRESS patients required ICU level care (8 [19%] of those hospitalized for DRESS treatment and 15 [68%] hospitalized for other reasons).

A median of 3 specialty consultant teams were involved in DRESS patients' care; median number of specialty consultants for patients hospitalized for DRESS syndrome (3 consultants [IQR, 2–5]) was lower than number of specialty consultants involved in care for patients hospitalized for other reasons (5.5 consultants [IQR, 2–7], $p=0.01$). There were 12 DRESS cases that were managed without Allergy/Immunology or Dermatology: 8 cases managed by Infectious Diseases, 2 managed by internal medicine hospitalists, 1 managed by a neurologist, and 1 managed by the primary care physician.

Two patients (3%) suffered an in-hospital death from sepsis; both patients had DRESS with kidney injury.

The estimated cost associated with DRESS syndrome that resulted in hospitalization was $17,101 2016 USD per patient.

## DISCUSSION

By using a free text search of the EHR allergy module, we identified 69 DRESS cases among 3.2 million people, corresponding to a PHS population prevalence of 2.18 per 100,000 patients. Organ injury included liver injury alone (42%) and renal injury alone (42%); 11 (16%) had both liver and renal injury. Drug culprits were most commonly antibiotics, with vancomycin responsible for approximately 40% of DRESS cases, and beta-lactams and anticonvulsants also frequently implicated. Almost half of the patients had two or more drugs as potential culprits. DRESS cases were morbid and resource-intensive; the patients hospitalized specifically for DRESS syndrome had a median length of stay of 9 days [IQR, 6 days-17 days], and cost of care exceeded $17,000 per patient.

Although few studies have reported prevalence or incidence of DRESS syndrome, a West Indian population identified an annual DRESS incidence of 0.9 in 100,000 people,[24] and a single center US study of inpatients discharged on over 14 days of parenteral antibiotics identified an incidence of 0.8%.[21] A retrospective study in Thailand over 11 years reported an incidence 9.63 cases per 100,000 inpatients.[25] The RegiSCAR study, which included multiple European countries over 6 years, found just 117 DRESS cases.[26] Using EHR free-text searching enabled DRESS case-finding in the EHR, with capture of 69 cases; 13% of retrieved HSRs were validated DRESS syndrome cases. Although more cases may have

been identified with broader search terms (e.g., review of a greater number of free text keywords or coded reactions), this increased sensitivity would result in reduced feasibility. Reviewing free text “drug reaction” and “drug rash” would have required review of over 1,20 0 HSRs and reviewing coded “rash” reactions would have required review of over 350,000 HSRs.[27]

In this study, we found that informatics methodologies were comparable, if not superior, to prior studies that used ICD-9/10 billing data to find cases of other SCARs. Validated Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) cases comprised a minority (less than 1.5%) of patients billed for the corresponding ICD-9/10 codes after EHR review.[28] Informatics methods, therefore, appear useful and practical for DRESS syndrome case identification; such methods may be broadly implemented on US EHRs to facilitate identification of national DRESS and SCAR cohorts.

One in five patients in this DRESS syndrome cohort had multiple organ injury, whereas prior data reported 50–60% of patients had two or more involved organs.[7] This observed difference may be due to increased recognition of DRESS syndrome by inpatient providers who monitor laboratory tests regularly, and specifically may monitor liver and kidney function in patients with rash and eosinophilia because of awareness of progression to DRESS syndrome. Similar to prior data, and despite using a more stringent definition of liver injury than RegiSCAR’s, [26] liver injury was the most common organ involved in DRESS.[10,11] However, other organ (e.g., lung, heart, etc.) injuries associated with DRESS syndrome were not identified in this study.[10,11] It is possible that alternative keywords (e.g., myocarditis) might have identified such cases. However, although our initial EHR search identified patients with lung injury, none of these patients ultimately met the specified DRESS syndrome criteria.

Antibiotics were the most common DRESS syndrome culprits. While one of the largest US case series similarly found that antibiotics were the most common cause of DRESS syndrome, that study identified sulfonamide antibiotics as the most common culprits, with over one third of patients having DRESS syndrome attributed to sulfamethoxazole.[32] Vancomycin, which has been previously described to cause DRESS syndrome,[33] was identified as the most common single drug culprit in this series. Similar to prior reports that identified a predisposition of allopurinol-induced DRESS syndrome to include renal injury, [4,8] we uniquely found that vancomycin-induced DRESS syndrome was more strongly associated with renal injury. While it is unclear why anticonvulsants were less commonly observed DRESS culprits in this study, possible explanations include improved screening for genetic associations (e.g., HLA-A*31:01 screening prior to carbamazepine) and/or provider awareness of anticonvulsants’ ability to cause DRESS and other SCARs, which may lead to immediate drug discontinuation with early HSR signs (e.g., rash only).

Although it is often challenging to identify the culprit drug for inpatients with non-immediate hypersensitivity reactions, the majority of DRESS patients in this study had only one drug identified as the culprit. This may be because these data come from hospitals that largely have immediate access to Dermatology and Allergy/Immunology consultants, who can (and did in all but 12 cases) assist in causality assessments. Still, despite this access,

one-third of patients had two or more drugs implicated and six patients had four or more drugs implicated. One prior study found that 10–20% of DRESS syndrome cases did not have an identified causative drug.[7] Having multiple drugs attributed to one HSR not only complicates future medical treatments, but also adds complexity to the EHR allergy module. These data emphasize the importance of using standardized causality assessments in the future, and highlights the need for improved confirmatory testing for DRESS syndrome.[29]

To our knowledge, this is the first study to estimate the resource utilization related to DRESS syndrome in a large US cohort. Almost all (95%) of DRESS patients were hospitalized, and in- hospital mortality was 3%. Among patients hospitalized specifically for DRESS syndrome treatment, median length of stay was 9 days and approximately 1 in 5 patients required ICU level care. While studies have described greater resources required for SJS and TEN, including a longer length of stay for SJS (4–25 days) and TEN (17–26 days), and more patients (>50%) requiring ICU level care,[30–33] DRESS syndrome is still clearly morbid and resource-intensive. The cost for DRESS syndrome that required hospitalization was at least $17,000 per patient, which is greater than the cost for hospitalizations associated with asthma admissions.[34,35] Additionally, our cost estimate relied only on the largest determinants of inpatient cost. If we had included other costs (e.g. pharmacy costs, outpatient costs), the estimate would have been even greater.

While we used defined keywords to identify DRESS cases, we may have missed true cases that were not found with our pre-specified informatics methods. Our DRESS case definition was stringent, and thus, we may have excluded true DRESS cases that did not meet our criteria. Although we specified DRESS syndrome criteria in advance of the study, consensus definitions do not exist for defining the liver and kidney injury in DRESS.[26,27] Because PHS is comprised of two academic tertiary care referral centers as well as several smaller, community-based hospitals, patients seen for their HSR at PHS were not always followed longitudinally by PHS. This meant that we were unable to use a complete RegiSCAR score or identify overall DRESS mortality (only in-hospital mortality). While we describe a large US DRESS syndrome cohort, 69 cases were often too few to draw conclusions between DRESS subgroups with different patterns of organ involvement. Finally, the analysis was performed with retrospective chart reviews, which can result in misclassification due to information bias.

In summary, we used a novel method to identify patients with DRESS syndrome listed in the allergy module of the EHR, which enabled identification of the largest US cohort of DRESS syndrome cases to date, with 69 patients. We described the clinical presentation of DRESS patients that will add to our knowledge base of this SCAR, including its common drug culprits, morbidity, and resource use. Future application of EHR search methods to other large US healthcare systems may help identify a nationally representative DRESS syndrome cohort for further study.

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## ABBREVIATIONS

| | |
|---|---|
| **DRESS** | Drug reaction with eosinophilia systemic symptoms |
| **EHR** | Electronic health record |
| **RegiSCAR** | European Registry of Severe Cutaneous Adverse Reactions [SCAR] to Drugs and Collection of Biological Samples |
| **IQR** | Interquartile range |
| **AHS** | Anticonvulsant Hypersensitivity Syndrome |
| **HSR** | Hypersensitivity reaction |
| **AEC** | Absolute eosinophil count |
| **ICD-9/10** | International Classification of Diseases, ninth/tenth edition |
| **SCAR** | Severe cutaneous adverse reaction |
| **PHS** | Partners HealthCare System |
| **REDCap** | Research Electronic Data Capture |
| **ICU** | Intensive care unit |
| **ALT** | Alanine aminotransferase |
| **USD** | United States Dollar |
| **Cr** | Creatinine |
| **SJS** | Stevens-Johnson syndrome |
| **TEN** | Toxic epidermal necrolysis |

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## HIGHLIGHTS BOX

1. What is already known about this topic?

DRESS syndrome is a rare but serious hypersensitivity reaction whose epidemiology in the US has been limited by case identification challenges. Electronic health records (EHRs) contain allergy lists, and informatics techniques could facilitate retrieval of relatively rare drug reactions.

2. What does this article add to our knowledge?

We identified 69 DRESS syndrome cases using informatics searching of the allergy list. Antibiotics were the most common culprits. Most DRESS patients were hospitalized (94%); hospitalizations for DRESS had median length of stay 9 days and cost over $17,000.

3. How does this study impact current management guidelines?

We used a new, reproducible methodology for DRESS case identification in EHRs that may facilitate identification of a large national cohort. Antibiotics may be the most common cause of DRESS syndrome in the United States (US). Management of DRESS syndrome for hospitalized patients costs at least $17,000 per patient.

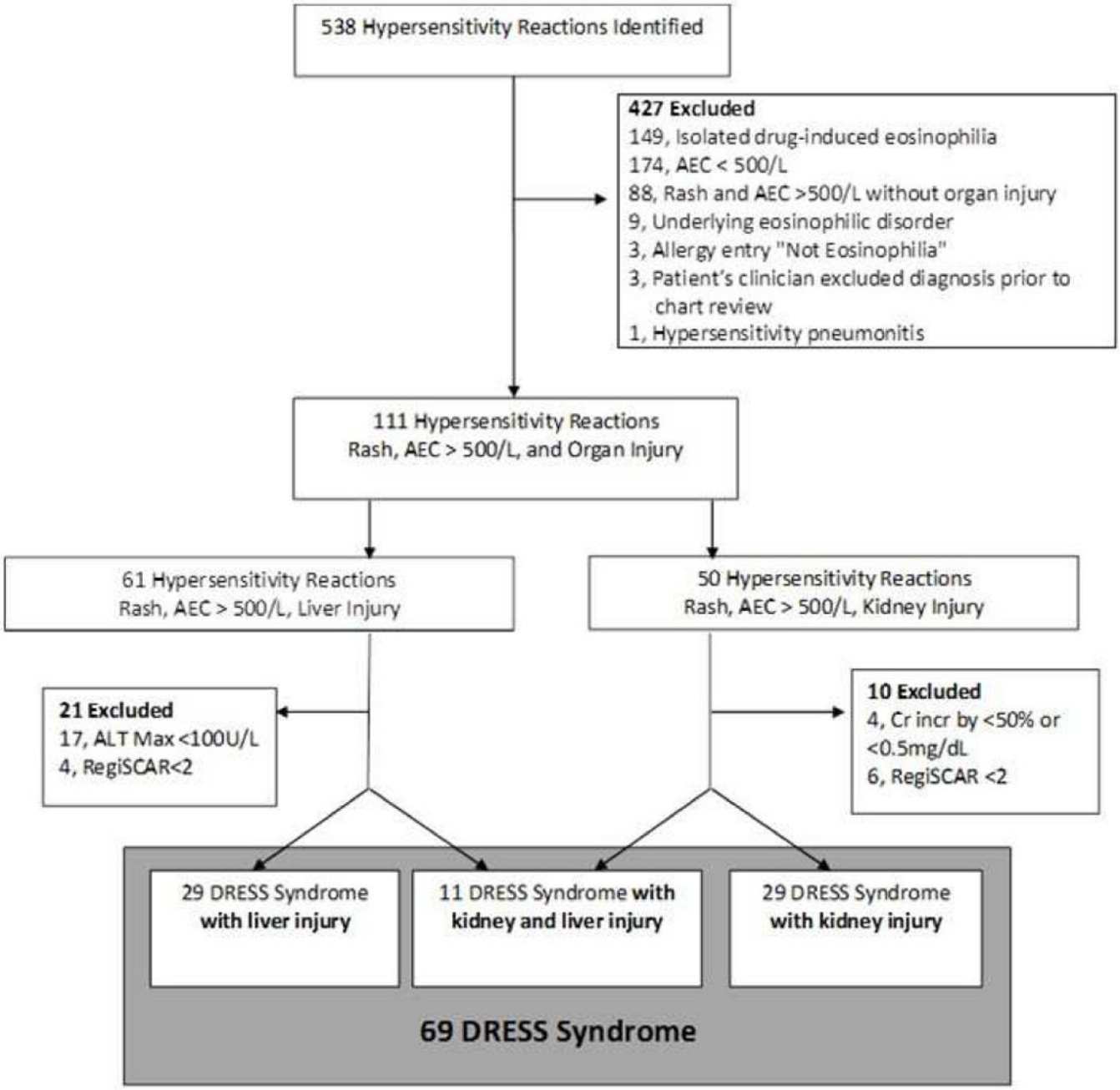


**Figure 1.**

Identification of 69 DRESS patients using the allergy module of the electronic health record. Keyword search identified 538 HSRs, of which 111 included rash, AEC of 500/L, and organ injury of any severity. Twenty-one patients with liver injury were excluded for not meeting established liver injury criteria: 17 did not meet our established liver injury criteria and 4 did not meet established RegiSCAR criteria. Ten patients with kidney injury were subsequently excluded: 4 did not meet our established kidney injury criteria and 6 did not meet established RegiSCAR criteria. The final cohort of DRESS syndrome included 69 patients

with DRESS syndrome: 29 involved liver injury, 29 involved kidney injury, and 11 involved both kidney and liver injury.

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**Table 1.**

Demographic and comorbid conditions of patients with DRESS syndrome (n=69)

| | |
|---|---|
| **Median Age in Years [IQR]** | 60 [41, 69] |
| **Female Sex, n (%)** | 38 (55) |
| **Race, n (%)** | |
| White | 49 (71) |
| Hispanic | 8 (12) |
| Black | 7 (10) |
| Asian | 3 (4) |
| Unknown | 2 (3) |
| **Comorbidities, n (%)** | |
| Hypertension | 38 (55) |
| Seizures | 13 (19) |
| Diabetes Mellitus | 12 (17) |
| Coronary Artery Disease | 9 (13) |
| Chronic Renal Disease or End-Stage Renal Disease | 8 (12) |
| Cancer* | 8 (12) |
| Asthma | 7 (10) |
| Autoimmune Disease† | 7 (10) |
| Congestive Heart Failure | 7 (10) |
| Substance Abuse‡ | 7 (10) |
| Bipolar Disorder | 6 (9) |
| Human Immunodeficiency Virus | 3 (4) |
| Chronic Obstructive Pulmonary Disease | 3 (4) |
| **Number of Comorbidities, n (%)** | |
| 0–1 | 31 (45) |
| 2–3 | 29 42) |
| ≥4 | 9 (13) |

*History of cancer, including currently in remission and including non-melanomatous skin cancers.

†Rheumatoid Arthritis (n=2); Psoriasis (n=2); Systemic Lupus Erythematosus (n=1); Ulcerative Colitis (n=1); Raynaud's Disease (n=1)

[‡] Heroin, alcohol and cocaine (n=1); alcohol (n=5); not specified (n=1).

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**Table 2.**

DRESS syndrome clinical characteristics

| | All DRESS Syndrome (n=69) | DRESS Syndrome with Liver Injury (n=29) | DRESS Syndrome with Kidney Injury (n=29) | DRESS Syndrome with Kidney and Liver Injury (n=11) | p-value |
|---|---|---|---|---|---|
| **Number of Drugs to which Reaction Attributed,** n (%) | | | | | |
| 1 | 38 (55) | 17 (59) | 15 (52) | 6 (55) | 0.77 |
| 2 | 16 (23) | 5 (17) | 7 (24) | 4 (36) | |
| 3 | 9 (13) | 5 (17) | 4 (14) | 0 (0) | |
| ≥4 | 6 (9) | 2 (7) | 3 (10) | 1 (9) | |
| **Drug,** * n (%) | | | | | |
| Antibiotics | 51 (74) | 21 (72) | 24 (83) | 6 (55) | 0.21 |
| Vancomycin | 27 (39) | 7 (24) | 16 (55) | 4 (36) | 0.06 |
| Penicillin | 9 (13) | 6 (21)§ | 2 (7)§§ | 1 (9) ¶¶ | 0.32 |
| Cephalosporin | 5 (7) | 2 (7)‖ | 2 (7)‖‖ | 1 (9) *** | |
| Tetracycline | 3 (4) | 3 (10)¶ | — | — | |
| Fluoroquinolone | 3 (4) | 1 (3) | 2 (7) | — | |
| Sulfonamide | 2 (3) | 2 (7) | — | — | |
| Carbapenem | 2 (3) | — | 2 (7) | — | |
| Anticonvulsant | 14 (20) | 6 (21) | 4 (14) | 4 (36) | 0.31 |
| Phenytoin | 7 (10) | 2(7) | 2 (7) | 3(27) | |
| Lamotrigine | 4 (6) | 2(7) | 1(3) | 1(14) | |
| Levetiracetam | 2 (3) | 1 (3) | 1 (3) | — | |
| Phenobarbital | 1 (1) | 1 (3) | — | — | |
| Allopurinol | 1 (1) | — | 1 (3) | — | |
| Other† | 3 (4) | 2 (7) | — | 1 (9) | |
| **RegiSCAR Score,** n (%) | | | | | |
| Possible DRESS (2–3) | 40 (58) | 16 (55) | 22 (76) | 2 (18) | |
| Probable DRESS (4–5) | 27 (39) | 11 (38) | 7 (24) | 9 (82) | |
| Definite DRESS (>5) | 2 (3) | 2 (7) | 0 (0) | — | |
| **Rash type,** n (%) | | | | | |

| | All DRESS Syndrome (n=69) | DRESS Syndrome with Liver Injury (n=29) | DRESS Syndrome with Kidney Injury (n=29) | DRESS Syndrome with Kidney and Liver Injury (n=11) | p-value |
|---|---|---|---|---|---|
| Maculopapular | 55 (79) | 25 (86) | 21 (72) | 9 (82) | 0.48 |
| Erythema | 40 (58) | 15 (52)** | 16 (55) | 9 (82) | 0.23 |
| Erythroderma | 3 (4) | 1 (3)†† | 2 (7) | — | |
| Purpura | 5 (7) | 2 (7)‡‡ | 2 (7) | 1 (9) | |
| Bullous | 2 (3) | — | 2 (7) | — | |
| Urticarial | 1 (1) | 1 (3) | — | — | |
| Unknown | 1 (1) | 1 (3) | — | — | |
| **AEC (/L),** median [IQR] | 1850 [890,3390] | 1679 [800, 3560] | 1931 [1135, 2800] | 1716 [1350, 4630] | 0.79 |
| **Creatinine (mg/dL),** median [IQR] | | | | | |
| Maximum Creatinine | — | — | 2.63 [1.87, 4.72] | 2.29 [1.74, 4.89] | 0.87 |
| Change in Creatinine | — | — | 1.44 [0.91, 3.68] | 1.08 [0.90, 1.20] | 0.13 |
| **ALT (U/L),** median [IQR] | | | | | |
| Maximum ALT | — | 226 [178, 457] | — | 234 [142, 458] | 0.84 |
| Change in ALT | — | 196 [159, 391] | — | 185 [114, 423] | 0.84 |
| **Corticosteroid use‡,** n (%) | 51 (74) | 20 (69) | 23 (79) | 8 (73) | 0.67 |
| Topical | 35 (51) | 13 (45) | 17 (59) | 5 (45) | 0.53 |
| Oral | 36 (52) | 17 (59) | 14 (48) | 5 (45) | 0.69 |
| Intravenous | 26 (38) | 7 (24) | 14 (48) | 5 (45) | 0.17 |

*If multiple drugs were implicated in the reaction, only the drug deemed most likely to be causative is listed (see methods).

†Other drugs included apitolisib (n=1), labetalol (n=1), and raltegravir (n=1).

‡Patients received more than one category of steroid.

§Amoxicillin-pot Clavulanate (n=2), Piperacillin-tazobactam (n=1), Amoxicillin (n=1), Augmentin (n=1), Ampicillin (n=1).

‖Ceftriaxone (n=1), Ceftazidime (n=1).

¶Minocycline (n=2), doxycycline (n=1).

**One patient had erythema alone.

††The patient also had a maculopapular rash.

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‡‡ One patient had purpura alone.

§§ Piperacillin-tazobactam (n=2).

‖‖ Ceftriaxone (n=1), cefoxitin (n=1).

¶¶ Penicillin VK (n=1).

*** Ceftazidime (n=1).

*Abbreviations:* DRESS, Drug Reaction with Eosinophilia and Systemic Symptoms; RegiSCAR, The European Registry of Severe Cutaneous Adverse Reactions (SCAR) to Drugs and Collection of Biological Samples; AEC, absolute eosinophil count; IQR, Interquartile Range; ALT, Alanine Aminotransferase.

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**Table 3.**

Hospitalized DRESS syndrome patients: Morbidity, mortality, and resource use (n=65)

| | All DRESS Syndrome (n=65) | Hospitalized for DRESS Syndrome (n=43) | DRESS Syndrome While Hospitalized for Other Reason (n=22) |
|---|---|---|---|
| **Discharge Diagnosis**, n (%) | | | |
| DRESS | 33 (51) | 33 (77) | — |
| Infection | 9 (14) | 3 (7)* | 6 (27)¶ |
| Respiratory Failure | 5 (8) | — | 5 (23) |
| Cardiac Disease | 5 (8) | 1 (2)† | 4 (18)** |
| Intracranial Hemorrhage | 3 (5) | 1 (2) | 2 (9) |
| Liver Disease | 3 (5) | 1 (2) | 2 (9) |
| Renal Failure | 2 (3) | 2 (5) | — |
| Retroperitoneal Hemorrhage | 1 (2) | 1 (2) | — |
| Other | 4 (6) | 1 (2)‡ | 3 (14)†† |
| **Specialty Consultants Involved in Diagnosis, n (%)** | | | |
| Dermatology | 52 (80) | 37 (86) | 15 (68) |
| Infectious Disease | 35 (54) | 25 (58) | 10 (45) |
| Allergy/Immunology | 29 (45) | 17 (40) | 12 (55) |
| Other | 5 (8) | 4 (9) | 1 (5) |
| **Total Number of Specialty Consultants Involved in Care**, median, [IQR] | 3 [2,6] | 3 [2, 5] | 5.5 [2, 7] |
| **Length of Stay (days)**, median [IQR] | 15 [7,30] | 9 [6, 17]§ | 36 [19, 43]§ |
| **Intensive Care Unit stay**, n (%) | 23 (35) | 8 (19) | 15 (68) |
| **Intensive Care Unit days‡‡**, median, [IQR] | 15 [4,29] | 3 [2.5, 4.5]‖ | 21 [12, 42]‖ |
| **In-Hospital Mortality**, n (%) | 2 (3) | 1 (2) | 1 (5) |
| **Estimated Cost** §§ | $50,646 | $17,101¶¶ | $84,606 |

*Sepsis (n=1); fevers and lymphadenopathy concerning for HIV and T cell lymphoma (n=1); fever (n=1).

†Congestive heart failure exacerbation (n=1).

‡ Altered mental status (n=1).

§ p<0.001

‖ p=0.01

¶ Bacteremia (n=1); wound infection (n=1); Endocarditis (n=1); AIDS (n=1); Post-operative wound infection (n=1); Prosthetic hip infection (n=1).

** Non-ischemic cardiomyopathy (n=1); Heart failure (n=1); Enterococcal aortic valve endocarditis and congestive heart failure (n=1); Cardiac arrest (n=1).

Status epilepticus (n=1); Seizure disorder(n=1); Traumatic injury (n=1).

†† Only included patients whose highest level of care was ICU.

$$\textit{Median Cost}_{HSR} = \textit{Median Cost/day}_{Medical/surgical} \times \textit{Median LOS}_{Medical/surgical} + \textit{Median Cost/day}_{ICU} \times \textit{Median LOS}_{ICU} + \textit{Initial Cost}_{Level\ 4\ Consult} \times N_{Consult} + 3(\textit{Subsequent Cost}_{Level\ 4\ consult} \times N_{consult})$$

‡‡ Estimated cost of DRESS Syndrome when it results in hospitalization.

*Abbreviations*: DRESS, Drug Rash Eosinophilia and Systemic Symptoms; IQR, Interquartile Range, HSR, Hypersensitivity Reaction

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