

# Severe cutaneous reactions to drugs in the setting of a general hospital\*

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**Abstract:** BACKGROUND: Cutaneous drug reactions are frequently found. Assessing the clinical and epidemiological profile of severe forms is extremely relevant for their better recognition and management. Few studies have assessed the severe forms of cutaneous drug reactions in patients hospitalized in our setting.

OBJECTIVES: To assess the clinical and epidemiological aspects of severe cutaneous adverse reactions to drugs in a tertiary hospital in Porto Alegre, Brazil.

METHODS: All cases of severe cutaneous adverse reactions to drugs in patients hospitalized from January/2005 to December/2010 were retrospectively analyzed for clinical and epidemiological variables. Cases of Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, drug hypersensitivity syndrome or Drug Reaction with Eosinophilia and Systemic Symptoms and acute generalized exanthematous pustulosis were included.

RESULTS: An occurrence rate of 1 serious reaction for every 3,048 inpatients was found (total of 173,767 inpatients admitted in the period). Drug Reaction with Eosinophilia and Systemic Symptoms was the most frequent presentation. The drugs most frequently involved were anticonvulsants (40.4%), antibiotics (26.3%), and analgesics/anti-inflammatory drugs (10.5%). Thirty seven patients (64.9%) were admitted to hospital because of the cutaneous drug reaction. Ten patients (17.5%) died and in most of those (60%), the drug causing the reaction could not be determined.

CONCLUSIONS: The frequency of severe cutaneous adverse reactions to drugs in our setting is significant. Drug Reaction with Eosinophilia and Systemic Symptoms seems to be the most frequent presentation of severe cutaneous drug reactions. Most patients developed cutaneous drug reactions outside the hospital. Mortality rates were higher for Toxic Epidermal Necrolysis and this presentation significantly affected older people. Not knowing the drug causing the reaction was related to mortality.

**Keywords:** Drug eruptions; Drug hypersensitivity; Stevens-Johnson Syndrome

## INTRODUCTION

Cutaneous drug reactions (CDR) comprise a heterogeneous group of dermatoses that can be part of a drug hypersensitivity systemic reaction.<sup>1</sup> Although the true incidence of these reactions is difficult to quantify, there are enough data to support that CDRs are among the most frequent adverse events resulting from drug treatment, reaching rates of up to 3% in hospitalized patients.<sup>2</sup>

According to the World Health Organization, severe cutaneous adverse reactions to drugs (SCARD) are those resulting in death, requiring hospitalization or those that extend the length of stay, result in persistent or significant disability or are life-threatening.<sup>3</sup> This group of drug reactions includes Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), drug hypersensitivity syndrome or DRESS (Drug Reaction with Eosinophilia and

Systemic Symptoms) and acute generalized exanthematous pustulosis (AGEP).<sup>4</sup>

Studies have shown that up to 6.7% of hospitalized patients present some degree of CDR, with the most severe forms ranging from 0.33% to 3%.<sup>5,6</sup> Few nation-wide studies have assessed the frequency of CDRs in hospitalized patients in Brazil. The few previous national studies show a low incidence of severe reactions, with absolute values of 2 or 3 cases for analysis periods ranging between about two to six years.<sup>7,8</sup>

Although these conditions are rare, knowledge of SCARD is warranted because of their great impact on morbidity and mortality rates, and on hospital costs. The purpose of this study is to assess clinical, epidemiological and etiological data on severe cutaneous drug reactions and check for possible connections between these factors and mortality.

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## MATERIAL AND METHODS

A retrospective study was conducted at the Clinical Hospital of Porto Alegre (Brazil), in which an assessment was made of all medical records of hospitalized patients with proven CDR who were seen at the Dermatology Department between January 2005 and December 2010. Severe reactions (SCARD) were defined as those causing hospitalization, that were fatal or life-threatening, or result in significant changes in the patient's treatment (presumably prolonged hospitalization). Based on morphology, distribution of lesions, and laboratory tests, SCARDs were classified into SJS, TEN, AGEP and DRESS cases. Patients who presented one of the severe reactions, even when an offending drug could not be determined due to the great number of drugs administered at the moment of diagnosis, were also included and considered for analyses.

The study variables were the following: age, gender, admission reason, type of cutaneous drug reactions (severe or non-severe), presentation pattern (SJS, TEN, DRESS, AGEP and other non-severe presentations), class of drug involved, time between drug administration and onset of reaction in days, concurrent medical conditions, medical and dermatological examination findings, results of laboratory tests, treatment established and outcome (death or resolution). Cases without appropriate available data were excluded.

The SPSS / Windows® (version 18.0) was used to perform descriptive analysis. Quantitative variables were expressed as a mean or median and categorical variables were described by absolute and relative frequencies. The association between categorical variables was assessed by Fisher's exact test. For polytomous variables, the association was estimated using the Monte Carlo method. The association between NET and age was evaluated by the Mann-Whitney test. Poisson regression analysis was used in order to adjust confounding factors. The alpha value of the study was 5%. The project was approved by the

Scientific Committee and the Ethics Review Board at the Clinical Hospital of Porto Alegre.

## RESULTS

During the study period, 173.767 patients were admitted to the hospital and 298 were diagnosed with CDR. Exanthem was the most frequent clinical presentation (52.3%) and 57 (19.1%) patients presented severe forms, with an estimated occurrence rate of one serious reaction for every 3,048 hospitalized patients. The severe forms were comprised of 26 DRESS cases (45.6%), 16 cases of TEN (28%), 13 cases of SJS (22.8%) and two cases of AGEP (3.5%).

The median age of patients affected by SCARD was 38.4 years, ranging from one month to 90 years of age. Virtually no difference in frequency was found between genders, with a male and female ratio of 1.1:1. The median time of exposure to the drug before the onset of the cutaneous reaction was 19.5 days.

Cutaneous drug reactions were the main reason for the admission of 37 patients (64.9%). The remaining 20 patients, who developed the condition during their hospital stay, were admitted for other reasons, with 9 of them presenting neurological diseases and 5 respiratory conditions.

Most patients (82.5%) had some concurrent clinical condition: 14 (24.6%) were hypertensive, 17 (29.8%) presented some sort of neuropsychiatric disorder and 10 (17.5%) were HIV positive. The characteristics of the patients affected by SCARD are shown in table 1.

With respect to the TEN cases, they affected significantly older people (75% were over 40;  $p=0.014$ ) and there was no difference in prevalence regarding gender ( $p=1.000$ ). When compared with other forms of severe skin reactions, there was a trend towards higher HIV positivity among those presenting this reaction ( $p = 0.098$ ). Hypertension, initially associated with NET, appeared as a confounding factor after adjustment for age ( $p = 0.334$ ).

TABLE 1: Characteristics of severe cutaneous drug reactions

	SJS*	TEN*	DRESS*	AGEP*
	n = 13	n = 16	n = 26	n = 2
Median age: years (min-max)	26 (0-81)	53 (4-90)	36.5 (1-71)	23 (18-28)
Median time to reaction: days (min-max)	10.5 (3-90)	16 (1-360)	21 (3-210)	1
Male:female ratio	1.6:1	1:1	1:1	1:1
Comorbidities n (%)	9 (69.2)	14 (87.5)	24 (92.5)	-
Main comorbidities n (%) <sup>a</sup>				
HBP**	1 (11.1)	7 (50)	6 (25)	-
HIV**	3 (33.3)	5 (37.7)	2 (8.3)	-
Neuropsychiatric disorder	4 (44.4)	2 (14.2)	11 (45.8)	-

\* SJS - Stevens-Johnson Syndrome; TEN - Toxic Epidermal Necrolysis; DRESS - Drug Reaction with Eosinophilia and Systemic Symptoms; AGEP - Acute Generalized Exanthematous Pustulosis

\*\* HBP - High Blood Pressure; HIV - Human immunodeficiency virus positive patients

† 1 month old

a - The percentages were calculated in relation to total comorbidities

In cases where the cause was determined, the most common suspected drug class was anticonvulsants, with 23 patients (40.4%) developing the reaction after using an antiepileptic drug. The second most frequent class of drug was antibiotics, with 13 cases (22.8%). Analgesics and anti-inflammatory drugs accounted for 6 cases (10.5%) of SCARD. In 10 patients (17.5%), the drug causing the cutaneous drug reactions could not be determined. Table 2 shows the distribution of severe cutaneous drug reactions, according to drug involved. Regarding the medications concerned, there was no significant difference between groups.

In most patients (82.5%), the outcome was resolution of their condition. Among the treatment measures taken, 54 (94.7%) patients had the suspected medication withdrawn, 22 (38.6%) required systemic steroids, 7 (12.3%) were administered antihistamines, 15 (26.3%) received antibiotics and only 2 patients (3.5%) were treated with intravenous immunoglobulin infusion. All patients who ultimately died due to critical illness, were admitted to intensive care units and had their potential offending drugs suspended. Only 3 of these patients received specific treatments: a DRESS patient on phenytoin was treated using oral prednisone (1mg/Kg/Day), the TEN case involving

dipyron received antibiotic therapy with vancomycin, while one of the TEN cases involving a non-identified drug received prednisone (1mg/Kg/Day), and systemic antibiotics.

Of the SCARD patients, 10 (17.5%) died. Out of these, 6 presented TEN, two SJS and two DRESS, which corresponded to mortality rates of 37.5%, 15.4% and 7.7%, respectively. Regarding outcome, patients with TEN died more frequently than patients affected by other cutaneous drug reactions ( $p=0.022$ ).

Of the deaths caused by TEN, one case was related to the use of dipyron, one to the use of sulfamethoxazole-trimethopim, and in four cases the causing drug could not be determined. Both deaths caused by DRESS were associated with the use of phenytoin. The drug causing the cutaneous drug reaction in the patients who died during the course of SJS could not be determined. Table 3 shows the characteristics of the patients who died.

Patients aged or under and those over 60 had higher mortality rates (22.2% and 44.4%, respectively) when compared with the age groups of 11-20, 21-40 and 40-60 years (with mortality rates of 0%, 6.3% and 16.7%, respectively). If patients were grouped in ages of 10 to 66 years old, there were significant differences

TABLE 2: Drugs causing the severe cutaneous drug reactions

	SJS* (22.8%)	TEN* (28.1%)	DRESS* (45.6%)	AGEP* (3.5%)	Drug-SCDR (n/%)‡
Antibiotics					
Penicillins	0	0	1 (3.8%)	1 (50%)	2 (3,5%)
Cephalosporins	0	0	1 (3.8%)	0	1 (1,75%)
Sulfonamides	1 (7.7%)	6 (37.5%)	1 (3.8%)	0	8 (14,03%)
Dapsone	0	0	1 (3.8%)	0	1 (1,75%)
Tuberculostatic	0	0	1 (3.8%)	0	1 (1,75%)
Anticonvulsants					
Phenytoin	1 (7.7%)	2 (12.5%)	5 (19.2%)	0	8 (14,03%)
Phenobarbital	2 (15.4%)	1 (6.2%)	0	0	3 (5,26%)
Carbamazepine	2 (15.4%)	0	10 (38.5%)	0	12 (21,05%)
Antirretrovirals					
Efavirenz	1 (7.7%)	0	1 (3.8%)	0	2 (3,5%)
Nevirapine	0	0	1 (3.8%)	0	1 (1,75%)
NSAIDS**					
Ibuprofen	1 (7.7%)	1 (6.2%)	0	1 (50%)	3 (5,26%)
Analgesics					
Dipyron	1 (7.7%)	1 (6.2%)	0	0	2 (3,5%)
Codeine	0	0	1 (3.8%)	0	1 (1,75%)
Endovenous contrast	0	0	1 (3.8%)	0	1 (1,75%)
Others					
Sibutramine	1 (7.7%)	0	0	0	1 (1,75%)
Unknown	3 (23.1%)	5 (31.3%)	2 (7.7%)	0	-
<b>Total (n)</b>	<b>13 (100%)</b>	<b>16 (100%)</b>	<b>26 (100%)</b>	<b>2 (100%)</b>	

\* SJS - Stevens-Johnson Syndrome; TEN - Toxic Epidermal Necrolysis; DRESS - Drug Reaction with Eosinophilia and Systemic Symptoms; AGEp - Acute Generalized Exanthematous Pustulosis

\*\* Non-steroidal anti-inflammatory drugs

‡ Total number of SCDR to specific drugs (n) with their overall contribution (%)

between the groups ( $p = 0.037$ ), and patients over 60 had a higher incidence of mortality.

## DISCUSSION

The frequency of SCARD varies widely among different studies. According to estimates, the incidence is 1.4 to 6 cases per one million patients a year.<sup>9</sup> These conditions cause significant morbidity and in the United States, they are the sixth cause of death in hospitalized patients.<sup>5</sup> In this study, an occurrence rate of 1 for every 3,048 hospitalized patients was found. This value is similar to the figures mentioned in previous reports.<sup>5,10,11</sup>

The proportion of SCARD was significantly higher than that found in other Brazilian publications, and was similar to rates mentioned in more recent international studies.<sup>7,8,11-13</sup> This could be due partly to the inclusion of DRESS cases, a cutaneous drug reaction that has been described more recently and which accounted for the largest number of cases in our sample. The predominance of the DRESS syndrome over other severe cutaneous drug reactions had already been shown in other publications. However, most studies that analyzed cutaneous drug reactions pointed to the predominance of SJS.<sup>5,7,8,11,14-17</sup>

The average age of the patients was 38.4 years, which is relatively young when compared with most studies on cutaneous drug reactions in general. In 2010, Huang *et al.* demonstrated a significantly younger average age ( $P < 0.001$ ) in patients with severe reactions, compared with non-severe reactions.<sup>13</sup> In our series, this fact could be attributed to the large share of young patients with neuropsychiatric disorders who

developed reactions due to the use of anticonvulsants, and the group of HIV-positive patients who developed the condition as a result of antiretroviral therapy or the treatment of opportunistic infections.

The offending drug was initiated on average three weeks before the skin reaction, similarly to previous reports, thus showing that drugs started within this timeframe should be the first to be suspected.<sup>18</sup>

SCARD is the main reason for the admission of most patients, i.e., the condition started outside the hospital setting. This information reinforces the importance of suspecting the diagnosis even in primary care settings like medical offices or emergency units, since early recognition of a reaction favorably influences the prognosis.<sup>19</sup>

Anticonvulsants, antibiotics and NSAIDs, as in most studies, were the main classes of drugs involved. There was no statistically significant difference between different medications and mortality.<sup>5,16,17</sup>

Regarding treatment measures, withdrawal of the suspected drug occurred in virtually all cases and systemic steroids and antibiotics were frequently administered. According to previous observational studies, the early withdrawal of the causing drug is proven to improve prognosis.<sup>19</sup> The use of steroids in the DRESS syndrome is generally satisfactory.<sup>20</sup> Steroid use in TEN and SJS cases is controversial and might be indicated only in the first 48 hours of the condition. Antibiotics are indicated in cases of severe cutaneous drug reactions whenever there is clinical suspicion or laboratory confirmation of secondary infection.<sup>8</sup>

In most patients (60%) who died, the offending drug that caused their reaction could not be determined, a fact that was significantly related to mortality ( $p = 0.001$ ). We could not gauge the exact time that drugs that had been administered were withdrawn in this scenario. However, a delay in withdrawing the drugs because they could not be determined may have contributed to unfavorable outcomes.

Our data seem to indicate that deaths by SCARD occur more often in children and the elderly. The trend towards increased mortality in older patients is well established.<sup>8</sup> However, due to the limited number of epidemiological studies, the frequency and prognosis of SCARD in children remain unknown. It is possible that impairments in the immune system or failures in drug metabolism contribute to an unfavorable prognosis in age extremes.<sup>6</sup>

The greater mortality rate caused by TEN has already been well described. Studies show a mortality rate of up to 50%, closely linked to the degree of skin detachment.<sup>4,9</sup>

Most patients with TEN were over 40 and the most commonly involved drugs were antibiotics, predominantly sulfonamides. In the analysis by

TABLE 3: Deaths caused by severe cutaneous drug reactions

	SJS*	TEN*	DRESS*
Deaths (n) – mortality rate (%)	2 (15.4%)	6 (37.5%)	2 (7.7%)
Male:female ratio	1:1	1:5	1:1
Age in years (min-max)	1-68	34-90	1-59
<b>Drug involved</b>			
Dipyron	0	1	0
Phenytoin	0	0	2
Sulfamethoxazole-trimethopim		1	0
Unknown	2	4	0
<b>Associated conditions‡</b>			
HBP**	1	4	1
DM**	0	1	1
CHF**	0	1	0
Nephropathy	0	2	0
Neuropsychiatric disorder	0	1	1
Lymphoma	0	1	0
COPD**	0	1	0
<b>Total number of cases</b>	<b>n = 13</b>	<b>n = 16</b>	<b>n = 26</b>

\* SJS – Stevens-Johnson Syndrome; TEN – Toxic Epidermal Necrolysis; DRESS – Drug

Reaction with Eosinophilia and Systemic Symptoms

\*\* HBP – High Blood Pressure; DM – Diabetes Mellitus; CHF – Congestive Heart Failure;

COPD – Chronic Obstructive Pulmonary Disease

‡ Note: Some patients were affected by more than one clinical condition



Rajartanam *et al.*, the average age was 53.5 years and the main classes involved were antibiotics, anticonvulsants and sulfonamides.<sup>21</sup> The connection between TEN and immunosuppressed states is well-established. HIV patients are 1,000 times more likely to develop TEN than the general population, a trend that was also noted in this study.<sup>3</sup>

## CONCLUSIONS

The frequency of SCARD in our setting was significant and similar to reports from different countries. DRESS syndrome was the most frequent clinical presentation. Anticonvulsants, antibiotics and analgesics/anti-inflammatories were the classes of drug most often involved. Most patients were admitted to hospital due to their cutaneous drug reactions, which

underscores the need to consider this condition even outside the hospital setting. Mortality rates were higher for TEN and this presentation significantly affected older people. In our series, the non-recognition of the causing drug was significantly related to mortality.

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