# Review of Culprit Drugs Associated with Patients Admitted to the Loyola University Medical Center Burn Unit with the Diagnosis of Stevens-Johnson Syndrome

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## Introduction

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis Syndrome (TENS) are severe and potentially lethal adverse reactions that affect the skin and mucous membranes. The reaction typically occurs within the first few weeks after the administration of an inciting agent (culprit drug) and is characterized by the inflammation of the skin and mucous membranes followed by keratocyte apoptosis and epidermal necrosis. This characteristic reaction is defined on a spectrum based on the percent of total body surface area with detachment (% TBSA): SJS (<10% TBSA), Overlap Syndrome (10-30%), and TENS (>30%).

Prior studies have identified several classes of culprit agents associated with SJS/TENS including antibiotics (sulfonamides), allopurinol, NSAIDs, anticonvulsants (carbamazepine) as well as others. A genetic predisposition to SJS/TENS has been attributed to specific HLA types and certain ethnic populations more likely to carry these alleles have been identified. For example, the HLA-B 15:02 allele—predominant in the Han Chinese—has been strongly associated with an increased risk of developing SJS following carbamazepine administration. As a result, HLA-B 15:02 screening of patients of Han Chinese descent has been recommended by the FDA.

## Objectives

The purpose of our study was to perform a systemic retrospective trend analysis of SJS spectrum diagnoses and culprit drugs in 147 patients admitted to the Loyola University Medical Center (LUMC) Burn Intensive Care Unit (BICU) over the past 15 years with the final diagnosis of SJS/TENS. The BICU at LUMC serves as a regional referral center for patients with suspected or confirmed SJS/TENS. These referrals came from the five other academic medical centers as well as private hospitals in the Chicagoland area.

## Methods

The electronic medical records (EMR) of patients as well as a database of patients seen at LUMC before EMR implementation were reviewed. Included patients were those with the diagnosis of SJS/TENS admitted to the LUMC BICU from 2002 to 2017. We used the well-established ALDEN algorithm to identify the most probable culprit drug in cases where multiple agents were involved. The following clinical data were reviewed: date of admission, SJS/TENS subtype diagnosis, biopsy confirmation, possible/probable inciting agents, and hospital mortality.

### Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN)

**Table 5 Details of the algorithm of drug causality for epidermal necrolysis (ALDEN)**

| Criterion | Values | Rules to apply | |
|---|---|---|---|
| Delay from initial drug component intake to onset of reaction (index day) | Suggestive +3 | From 5 to 28 days | −3 to 3 |
| | Compatible +2 | From 29 to 56 days | |
| | Likely +1 | From 1 to 4 days | |
| | Unlikely −1 | >56 Days | |
| | Excluded −3 | Drug started on or after the index day | |
| | | In case of previous reaction to the same drug, only changes for: Suggestive: +3; from 1 to 4 days Likely: +1; from 5 to 56 days | |
| Drug present in the body on index day | Definite 0 | Drug continued up to index day or stopped at a time point less than five times the elimination half-life[a] before the index day | −3 to 0 |
| | Doubtful −1 | Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a] but liver or kidney function alterations or suspected drug interactions[b] are present | |
| | Excluded −3 | Drug stopped at a time point prior to the index day by more than five times the elimination half-life[a], without liver or kidney function alterations or suspected drug interactions[b] | |
| Prechallenge/rechallenge | Positive specific for disease and drug: 4 | SJS/TEN after use of same drug | −2 to 4 |
| | Positive specific for disease or drug: 2 | SJS/TEN after use of similar[c] drug or other reaction with same drug | |
| | Positive unspecific: 1 | Other reaction after use of similar[c] drug | |
| | Not done/unknown: 0 | No known previous exposure to this drug | |
| | Negative −2 | Exposure to this drug without any reaction (before or after reaction) | |
| Dechallenge | Neutral 0 | Drug stopped (or unknown) | −2 or 0 |
| | Negative −2 | Drug continued without harm | |
| Type of drug (notoriety) | Strongly associated 3 | Drug of the "high-risk" list according to previous case–control studies[d] | −1 to 3 |
| | Associated 2 | Drug with definite but lower risk according to previous case–control studies[d] | |
| | Suspected 1 | Several previous reports, ambiguous epidemiology results (drug "under surveillance") | |
| | Unknown 0 | All other drugs including newly released ones | |
| | Not suspected −1 | No evidence of association from previous epidemiology study[d] with sufficient number of exposed controls[c] | |
| | | Intermediate score = total of all previous criteria | −11 to 10 |
| Other cause | Possible −1 | Rank all drugs from highest to lowest intermediate score | −1 |
| | | If at least one has an intermediate score >3, subtract 1 point from the score of each of the other drugs taken by the patient (another cause is more likely) | |
| Final score −12 to 10 | | | |

<0, Very unlikely; 0–1, unlikely; 2–3, possible; 4–5, probable; ≥6, very probable.

ATC, anatomical therapeutic chemical; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

[a]Drug (or active metabolite) elimination half-life from serum and/or tissues (according to pharmacology textbooks, tentative list available in complementary table), taking into account kidney function for drugs predominantly cleared by kidney and liver function for those with high hepatic clearance. [b]Suspected interaction was considered when more than five drugs were present in a patient's body at the same time. [c]Similar drug = same ATC code up to the fourth level (chemical subgroups), see Methods. [d]See definitions for "high risk," "lower risk," and "no evidence of association" in Methods, ref. 15 (detailed list available in complementary table).

Table above reprinted from: Sassolas, B., *et al.* ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case-control analysis. *Clin Pharmacol Ther* **88**, 60-68 (2010).

## Results

**Table 1: Patient demographics and clinical characteristics**

| | Overall n=147 | SJS n=47 | Overlap n=27 | TENS n=73 |
|---|---|---|---|---|
| **Age, mean (SD)** | 43.9 (22.9) | 43.7 (22.7) | 47.2 (17.5) | 42.8 (25.0) |
| **Female, n (%)** | 83 (56.5) | 29 (61.7) | 18 (66.7) | 36 (49.3) |
| **Race, n (%)** | | | | |
| **Asian** | 15 (10.2) | 7 (14.9) | 2 (7.4) | 6 (8.2) |
| **African American** | 53 (36.1) | 18 (38.3) | 12 (44.4) | 23 (31.5) |
| **White** | 65 (44.2) | 14 (29.8) | 13 (48.1) | 38 (52.1) |
| **Other** | 13 (8.8) | 8 (17.0) | 0 (0.0) | 5 (6.8) |
| **Multiracial** | 1 (0.7) | 0 (0.0) | 0 (0.0) | 1 (1.4) |
| **Year admitted to BICU, n (%)** | | | | |
| **2002-2005** | 10 (6.8) | 0 (0.0) | 1 (3.7) | 9 (12.3) |
| **2006-2009** | 38 (25.9) | 5 (10.6) | 11 (40.7) | 22 (30.1) |
| **2010-2013** | 45 (30.6) | 12 (25.5) | 9 (33.3) | 24 (32.9) |
| **2014-2017** | 54 (36.7) | 30 (63.8) | 6 (22.2) | 18 (24.7) |
| **Inciting drug listed, n (%)** | 98 (66.7) | 38 (80.9) | 11 (40.7) | 49 (67.1) |

**Table 2: Culprit drugs by spectrum diagnosis**

| | Overall n=98 | SJS n=38 | Overlap n=11 | TENS n=49 |
|---|---|---|---|---|
| **Primary inciting drug n (%)** | | | | |
| **Anticonvulsant** | 24 (24.5) | 10 (26.3) | 2 (18.2) | 12 (24.5) |
| **NSAID** | 9 (9.2) | 1 (2.6) | 0 (0.0) | 8 (16.3) |
| **Fluoroquinolones** | 14 (14.3) | 6 (15.8) | 3 (27.3) | 5 (10.2) |
| **Allopurinol** | 11 (11.2) | 5 (13.2) | 1 (9.1) | 5 (10.2) |
| **Sulfa Drugs** | 9 (9.2) | 6 (15.8) | 0 (0.0) | 3 (6.1) |
| **Immunosuppressants** | 2 (2.0) | 0 (0.0) | 0 (0.0) | 2 (4.1) |
| **Other** | 29 (29.6) | 10 (26.3) | 5 (45.5) | 14 (28.6) |

***n=49 did not have a primary inciting drug identified, omitted above

**Figure 1: Culprit Drugs by Year**

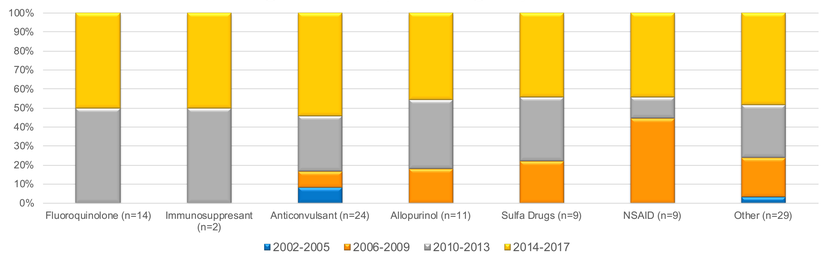


**Table 3: Culprit drugs by year**

| | 2002-2005 n=3 | 2006-2009 n=16 | 2010-2013 n=31 | 2014-2017 n=48 |
|---|---|---|---|---|
| **Anticonvulsant (n=24)** | 2 | 2 | 7 | 13 |
| **Fluoroquinolones (n=14)** | 0 | 0 | 7 | 7 |
| **Allopurinol (n=11)** | 0 | 2 | 4 | 5 |
| **Sulfa Drugs (n=9)** | 0 | 2 | 3 | 4 |
| **NSAID (n=9)** | 0 | 4 | 1 | 4 |
| **Immunosuppressant (n=2)** | 0 | 0 | 1 | 1 |
| **Other* (n=29)** | 1 | 6 | 8 | 14 |

- The reviewed cases were divided into four groups based on year: 2002-2005, 2006-2009, 2010-2013, and 2014-2017.
- 147 patients were admitted to the BICU with a biopsy-confirmed spectrum disorder from 2002-2017.
- In 98 of 147 patients seen from 2002-2017 with a biopsy-confirmed spectrum disorder, a clear probable inciting agent was able to be determined.

## Discussion

In patients admitted to LUMC from 2002-2017 with a biopsy-confirmed SJS/TENS spectrum diagnosis (n=147), the most common spectrum classification was TENS (n=73), followed by SJS (n=46) and Overlap Syndrome (n=27). Of the 98 cases between 2002-2017 in which a single probable culprit drug was able to be identified, anticonvulsants (n=24), fluoroquinolones (n=14), allopurinol (n=11), sulfa drugs (n=9), and NSAIDs (n=9) were the most common inciting agents. In our study population, the incidence of anticonvulsant-induced reactions increased significantly from 2002-2017. Additionally, the incidence of fluoroquinolone-induced reactions increased from 2006-2017. Available information on %TBSA and other relevant clinical data from cases that fell within the 2002-2005 time interval was limited. Thus, SJS spectrum classifications as well as a single probable inciting agent could not be accurately determined for many of these cases. We hope that by tracking inciting agents in future cases we will be able to determine the most probable inciting agent using ALDEN in the context of clinical presentation–with more accurate and accessible information available through EMR. Trends in culprit drugs can shift over time based on changes in prescribing practices. Different inciting agents may lead to more or less severe presentations of SJS/TENS spectrum reactions. Therefore, these trends need to be monitored in order to advise providers on which agents present the greatest risk to patients.

## Conclusions

- This is one of the largest single center series of SJS/TENS/Overlap cases in the US.
- In Loyola/Chicagoland patients admitted to LUMC, anticonvulsants, fluoroquinolones, allopurinol, and sulfamethoxazole/trimethoprim continue to be common probable culprit drugs.
- For the Loyola/Chicagoland region, the incidence of anticonvulsants as a probable culprit drug has increased significantly from 2002-2017.
- NSAIDs were the second most common inciting agents in patients presenting with TENS.
- Between 2006-2017 there has been an increased proportion of patients presenting with SJS as well as a decreased proportion of patients presenting with TENS.
- For the more severe TENS cases, the anti-convulsant lamotrigine was the most common inciting agent.
- Our data supports trends presented in the EuroSCAR (1997-2001) and RegiSCAR (2003-2012) studies.
- The ALDEN algorithm provides an important and validated method for determining the probable culprit drug in SJS/TENS spectrum reactions.

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