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**Title:** Developing a skin-directed Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis scoring system, A modified Delphi consensus exercise

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**Abstract: 298 WORDS**

*Background:* Existing scoring systems for Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) only measure patient prognosis and are heavily weighted towards comorbidities and systemic features. Further, terminology in this disease is not consistent, and it is unclear if certain skin locations are disproportionately affected.

*Objective*: To establish consensus among expert dermatologists in disease terminology, morphologic progression, and typical locations for SJS/TEN, and to use this consensus as a framework to guide the development of a skin-directed scoring assessment in SJS/TEN.

*Methods:* A modified Delphi consensus using the RAND/UCLA appropriateness criteria was initiated with a core group of members from the Society of Dermatology Hospitalists. The intent of the first exercise is to establish agreement on the optimal design for a cutaneous scoring instrument, as well as agreement on terminology, morphologies, and locations of involvement.

*Results:* Fifty-four dermatology hospitalists agreed to participate in this study. After one round, all statements reached consensus (agreement on 30 appropriate, 3 inappropriate, and 16 uncertain statements). A subsequent round was conducted, at which point, 15 uncertain statements reached agreement (8 appropriate and 7 uncertain statements). Participants consistently agreed on the need of such an instrument. Locations including the head and neck, chest, upper back, ocular mucosa, and oral mucosa were agreed to be almost always affected by SJS/TEN. Agreement was also reached in morphologic terminology, namely that blanching erythema, dusky erythema, targetoid erythema, vesicles/bullae, desquamation, and erosions can be consistently differentiated and encompass the morphologies present in the disease.

*Conclusions:* This consensus exercise has established that there is widespread agreement among expert dermatologists in a need for a skin directed scoring system, nomenclature and differentiation of specific morphologies, and that some locations are more likely than others to be involved. This undertaking has so far revealed a need for this instrument and provided consistent terminology to be used in SJS/TEN.

**Capsule summary: 82 WORDS**

**What is Known:** SCORTEN and ABCD-10 are validated scoring systems for prognosis of patients with SJS/TEN.

**What this study adds**: Agreement in the need for a revised disease assessment tool, morphologies present, their terminology, and locations of disease.

**Implications for Practice:** These terms should be used for clinical practice and set the stage for a skin-directed scoring system to assess skin disease severity, progression, and improvement in SJS/TEN. This study sets the stage for improved consistency in documenting morphologies present and establishes further need for a skin directed scoring instrument in SJS/TEN.

**Introduction:**

Stevens Johnson Syndrome and Toxic Epidermal Necrolysis (SJS/TEN) are severe adverse cutaneous drug reactions with life threatening implications.1,2 Other sites of involvement include both acute and chronic ocular, oropharyngeal, respiratory, genital, and mucous membranes involvement, while psychological impacts and chronic sequelae may occur.3 Prognostic models such as the SCORTEN and ABCD-10 are traditionally calculated within 24 hours of admission to assess risk of mortality.4,5,6 Although both scores have excellent discriminatory power, the SCORTEN and ABCD-10 are not intended to assess disease progression and improvement.7 Recognizing the lack of sensitive tools to assess SJS/TEN disease severity, we conducted a structured exercise to assess agreement among experts on SJS/TEN morphologies, sites of involvement, locations, and the need for a skin severity tool.

**Methods:**

**Panel selection**

Experts were required to currently practice as a dermatology hospitalist, with attending physician privileges at tertiary centers that care for SJS/TEN patients with a minimum of four years of experience and at least one SJS/TEN patient seen per year. In total, 159 members of the Society of Dermatology Hospitalists Listserv were invited by email to participate in the exercise and a total of 54 experts were qualified and accepted.

**First Round**

Participants were sent an online list of 49 statements regarding SJS/TEN. Surveys were administered online via SurveyMonkey. First round statements were designed to assess the need for a skin-directed assessment for SJS/TEN, obtain a consensus of SJS/TEN sites of involvement and disease-associated skin morphologies (Supplemental Appendix Table). Participants were asked to evaluate the level of appropriateness of statements on a scale of 1 (extremely inappropriate) to 9 (extremely appropriate). Participants were given the option of selecting “N/A” (not applicable) if they felt they did not have the necessary expertise to rank a particular statement. Participants also had the opportunity to submit comments after each set of questions to be incorporated into subsequent rounds.

**Second Round**

Comments collected during the first round were used to revise statements that the panel agreed were of uncertain appropriateness. The revised statements, the associated original statements, and respective DI and mean were then presented to the experts in the second Delphi round. Statement additions, changes, and flow are highlighted in Figure 1.

**Statistical Approach**

Results were analyzed using the RAND/UCLA Appropriateness Method.8 The median rating for appropriateness, interpercentile range (IPR), interpercentile range adjusted for symmetry (IPRAS), and disagreement index (DI) were calculated (DI=IPR/IPRAS) for each statement.9 A median appropriateness value of 1.0 to 3.4 was considered “inappropriate”, 3.5 to 6.9 as “uncertain”, and 7.0 to 9.0 as “appropriate, a disagreement index (DI) value greater than or equal to 1.0 indicated a lack of consensus among the participants regarding the statement’s appropriateness.8

**Results:**

**Participants**

All 54 participants responded to the first Delphi questionnaire (100% response rate) and second round (100% response rate). Participants were from 43 different institutions in the United States (n = 42) and United Kingdom (n = 1). Demographics of the respondents are presented in Table 1. Of the 54 respondents, the median (IQR) practice time was 10 (5.3) years, with 2 (4) publications in SJS/TEN and 6 (8) patients seen per year (Table 1).

**First Round**

All statements (49/49) reached consensus (100%). All statements and their respective DI and median are displayed in Table S1. Thirty statements were agreed upon as appropriate, 3 statements were agreed upon as inappropriate, and 16 statements were agreed upon as uncertain.Consensus was reached that the ABCD-10 and SCORTEN are inappropriate tools to detect changes in skin severity, and that there is a need for a cutaneous scoring instrument to monitor SJS/TEN disease course.

Certain body locations, including the head and neck, chest, upper back, ocular mucosa, and oral mucosa were agreed to almost always affected by SJS/TEN. It was agreed upon that specific SJS/TEN morphologies that could be differentiated from other morphologies seen in SJS/TEN included blanching erythema, dusky erythema, targetoid erythema, atypical targetoid erythema, vesicles/bullae, desquamation, erosions, re-epithelialized skin, mucosal bullae, and mucosal erosions.

**Second Round**

During the second round, participants reached consensus on all (15/15) revised statements. Eight statements were agreed upon as appropriate and seven were agreed upon as uncertain (Table S2). In total, after two rounds, 48 statements reached consensus. Thirty-eight statements were agreed upon as appropriate, 3 statements were agreed upon as inappropriate, and 7 statements were agreed upon as uncertain (Tables 2-4).

**Discussion:**

The aim of this Delphi exercise was to establish consensus among expert dermatologists regarding the need for a revised SJS/TEN skin severity tool while establishing SJS/TEN-associated disease terminologies, e.g., morphologic differentiations, and sites of SJS/TEN involvement. This information will be critical in future structured consensus exercises designed to provide a framework to guide the development of a skin-directed disease severity assessment for SJS/TEN.

**Unmet Need**

Consensus was obtained in key fields to confirm that there is a need for an SJS/TEN skin-directed disease severity scoring tool. Participants agreed that the use of the ABCD-10 and SCORTEN to detect changes in disease severity was inappropriate. Additionally, the use of a BSA of greater or less than 10% as a sufficient evaluation of disease severity was also agreed as inappropriate.There was agreement that an instrument to assess SJS/TEN mucocutaneous severity at baseline and monitor changes is necessary. This tool should be used to assess disease severity at patients’ initial presentation as well as daily until discharge. There was further agreement regarding characteristics of the disease assessment tool, including that it should be that such a tool should be optimized toward a hospital setting by having an online interface that does not require a calculator to use, and it should include body surface area of involvement, differentiate specific disease morphologies present, and offer prototypical images as guiding examples. It was agreed upon that such a tool is necessary for future clinical trials in SJS/TEN.

**Locations of Involvement**

Multiple locations were noted to almost always be present (Table 3). Notably, much of the agreed upon uncertainty from the first round was in reference to a specific location and the use of “almost always” in the statement. First round statements were designed to limit ambiguity and vagueness, as has been deemed critical in developing consensus statements.10 However, when consensus could not be obtained, the language was softened, by modifying involvement as “almost always” to “usually.” With this substitution, participants were in agreement that SJS/TEN “usually” affects the abdomen, lower back, anterior arms, and genitalia.

These results are noteworthy because very few existing publications detail the areas and time of progression of cutaneous and mucosal involvement for SJS/TEN. One review by Wong et. al detailed areas where lesions are typically found,11 and another by French and colleagues specified that cutaneous lesions tended to appear first on the trunk, later spreading to the neck, face, and proximal upper extremities.12 Most articles more generally describe SJS/TEN as affecting the skin, mucosa, genitalia, and respiratory tract without specifying which areas of the body are most severely or most commonly affected.13,14 When specific sites are mentioned, they usually detail the mucosal involvement, including the oropharynx, conjunctiva, genitalia, and/or anus, but rarely cutaneous body locations.15 Our exercise corroborates existing descriptions by French and Wong et. al,11,12 and also more summarizes the typical distribution of SJS/TEN.

**Morphologies**

Compared to sites of involvement, descriptions of SJS/TEN lesion morphology are more commonly documented in the literature, but not necessarily agreed upon. Several studies have described the major morphologic manifestations of SJS/TEN, including typical and atypical targetoid lesions, vesicles and bullae, desquamation, and erosions for cutaneous morphologies and included mucosal bullae and erosions for mucosal morphologies.16 Additionally, several studies have detailed the mucosal involvement and morphologies of SJS/TEN.12,16,17 A study by Assier et al, pointed out that the widespread flat atypical targets and purpuric macules were very common cutaneous manifestations that help distinguish SJS/TEN from other eruptions such as erythema multiforme.17 A study by Brockow et. al emphasized that SJS/TEN can be differentiated from other cutaneous drug eruptions by its dusky red macules and flat atypical target lesions, which evolve quickly to bullae and skin detachment.18 Notably, our participants highlight that early SJS/TEN presents with blanching erythema that can be distinguished from other cutaneous morphologies. Similarly, fixed erythema, targetoid erythema, atypical targetoid erythema, vesicles/bullae, desquamation, erosions, and re-epithelialized skin morphologies were also distinguishable. However, our panel was uncertain about several mucosal morphologies. Specifically, it was unclear if dusky mucosal erythema, mucosal erythema, and re-epithelialization of mucosa could reliably be distinguished from each other in SJS/TEN.

Our exercise provides useful knowledge of the spectrum of SJS/TEN morphologies and importantly adds early blanching erythematous macules to the literature. Future work needs to validate that these morphologies and locations are distinguishable, while establishing the impact of these morphologies and their progression.

**Conclusion:**

Our panel broadly agreed in an overall need for a skin severity assessment tool, terminology, locations, and morphologies. We anticipate this work will impact many areas of SJS/TEN, including existing clinical trials studying the disease and terminology. It may also impact the terminologies and foundation trainees learn to describe and diagnose morphologies seen in the disease. We are hopeful that it will help improve standardization of documenting disease progression, the characterization and management of this disease, and serve as a basis for the development of future outcomes measurements to measure the severity and change in SJS/TEN.

**Abbreviations:**

SJS/TEN – Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis

SCORTEN – Severity-of-Illness Score for Toxic Epidermal Necrolysis

ABCD-10 – Age, Bicarbonate, Cancer, Dialysis, 10% Body Surface Area

DI – Disagreement Index

IPR – Interpercentile Range

IPRCP – Interpercentile Range Central Point

IPRAS – Interpercentile Range Adjusted for Symmetry

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**Figure Legend**

Figure 1: Flowchart illustrating the work steps of the Delphi exercise

Diagram

Description automatically generated

|  |  |  |  |
| --- | --- | --- | --- |
|  | Mean | Median | Interquartile Range |
| Years of dermatology practiced | 10.7 | 10.0 | 5.3 |
| SJS/TEN cases seen per year | 8.3 | 6.0 | 8.0 |
| Previous SJS/TEN publications | 3.0 | 2.0 | 4.0 |

Table 1A: Demographics: Experience

Table 1B: Demographics: Geography

|  |  |
| --- | --- |
| United States Geographical Region\* | n |
| Northeast | 13 (24%) |
| Midwest | 15 (28%) |
| South | 14 (26%) |
| West | 11 (20%) |

Not included: United Kingdom (n=1; 2%)

\*Regions defined by the United States Census Bureau

Northeast: Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, and Pennsylvania

Midwest: Illinois, Indiana, Michigan, Ohio, and Wisconsin, Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, and South Dakota

South: Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, Washington D.C., West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, and Texas

West: Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming, Alaska, California, Hawaii, Oregon, and Washington

**Table 2. Items the panel agreed upon regarding the need for a cutaneous scoring instrument and general statements about SJS/TEN**

|  |  |
| --- | --- |
|  | Rating (A/I/U)\* |
| **Need and General Statements** | |
| Every SJS/TEN patient should have a daily skin assessment until hospital discharge. | **A** |
| An instrument to assess SJS/TEN mucocutaneous severity at initial presentation is needed. | **A** |
| An instrument to monitor changes in SJS/TEN mucocutaneous severity is needed. | **A** |
| An instrument based on the “rule of 9s” is the simplest method of estimating body surface area. | **A** |
| Neither the ABCD-10 nor the SCORTEN is superior to one another. | **A** |
| The “rule of 9s” is the most widely used method of estimating body surface area. | **A** |
| The “rule of 9s” is preferable to the handprint method for estimating body surface area in SJS/TEN. | **A** |
| The SCORTEN is a useful tool to detect a change in skin severity. | **I** |
| The ABCD-10 is a useful tool to detect a change in skin severity. | **I** |
| Body surface area greater or less than 10% epidermal detachment is a sufficient assessment of SJS/TEN disease severity. | **I** |

**Table 3: Items the panel agreed upon regarding the locations of SJS/TEN**

|  |  |
| --- | --- |
|  | Rating (A/I/U)\* |
| **Locations** | |
| SJS/TEN can occur on any mucocutaneous surface of the body. | **A** |
| SJS/TEN has a predilection for specific areas of the body. | **A** |
| SJS/TEN almost always affects the head and neck. | **A** |
| SJS/TEN almost always affects the chest. | **A** |
| SJS/TEN almost always affects the upper back. | **A** |
| SJS/TEN almost always affects the oral mucosa. | **A** |
| SJS/TEN almost always affects the ocular mucosa. | **A** |
| SJS/TEN usually affects the abdomen. | **A** |
| SJS/TEN usually affects the lower back. | **A** |
| SJS/TEN usually affects the anterior arms. | **A** |
| SJS/TEN usually affect the genitalia. | **A** |
| SJS/TEN usually affects the posterior arms. | **U** |
| SJS/TEN usually affects the anterior legs. | **U** |
| SJS/TEN usually affects the posterior legs. | **U** |
| SJS/TEN usually affects the palms. | **U** |
| SJS/TEN usually affects the soles of the feet. | **U** |
| SJS/TEN usually affects the anal mucosa. | **U** |

**Table 4: Items the panel agreed upon regarding the morphologies of SJS/TEN**

|  |  |
| --- | --- |
|  | Rating (A/I/U)\* |
| **Morphologies** | |
| Blanching erythema usually can be differentiated from other cutaneous morphologies seen in SJS/TEN. | **A** |
| Dusky/fixed erythema usually can be differentiated from other morphologies in SJS/TEN. | **A** |
| Targetoid erythema usually can be differentiated from other morphologies in SJS/TEN. | **A** |
| Atypical targetoid erythema usually can be differentiated from other morphologies in SJS/TEN. | **A** |
| Vesicles and bullae usually can be differentiated from other morphologies in SJS/TEN. | **A** |
| Desquamation usually can be differentiated from other morphologies in SJS/TEN. | **A** |
| Erosions usually can be differentiated from other morphologies in SJS/TEN. | **A** |
| Re-epithelialized skin usually can be differentiated from other morphologies in SJS/TEN. | **A** |
| Mucosal bullae usually can be differentiated from other mucosal morphologies in SJS/TEN. | **A** |
| Mucosal erosions usually can be differentiated from other mucosal morphologies in SJS/TEN. | **A** |
| Mucosal erythema that occurs in SJS/TEN cannot be reliably distinguished into severe (or dusky) or early. | **A** |
| Mucosal erythema that occurs in SJS/TEN can be reliably distinguished from other mucosal morphologies including vesicles, blisters, and erosions. | **U** |

\* The rating of A/I/U represents whether the participants found the statement appropriate (A), inappropriate (I), or uncertain (U).

**Supplemental**

**Table S1.** All statements from round one

|  |  |  |
| --- | --- | --- |
|  | Disagreement index (DI) \* | Median |
| **Statements that the panel agreed were “appropriate”.** | | |
| Skin assessment and prognostic tools, such as SCORTEN/ABCD-10, should be completed for every SJS/TEN patient. | **0.13** | 9 |
| The SCORTEN is a useful prognostic tool. | **0.16** | 7 |
| The ABCD-10 is a useful prognostic tool. | **0.22** | 7 |
| Every SJS/TEN patient should have a daily skin assessment until hospital discharge. | **0.13** | 9 |
| An instrument to assess SJS/TEN mucocutaneous severity at initial presentation is needed. | **0.29** | 8.5 |
| An instrument to monitor changes in SJS/TEN mucocutaneous severity is needed. | **0.13** | 9 |
| An ideal SJS/TEN mucocutaneous disease assessment tool should be no more than a single page in length. | **0.00** | 9 |
| An ideal SJS/TEN mucocutaneous disease assessment tool should be an online application. | **0.21** | 7 |
| An ideal SJS/TEN mucocutaneous disease assessment tool should not require a calculator to complete. | **0.46** | 8 |
| An ideal SJS/TEN mucocutaneous disease assessment tool should include body surface area. | **0.00** | 9 |
| An ideal SJS/TEN mucocutaneous disease assessment tool should include disease morphology. | **0.49** | 7.5 |
| An ideal SJS/TEN mucocutaneous disease assessment tool should provide example images to help assess disease morphology. | **0.29** | 8 |
| An instrument based on the “rule of 9s” is the simplest method of estimating body surface area. | **0.29** | 8 |
| SJS/TEN can occur on any mucocutaneous surface of the body. | **0.00** | 9 |
| SJS/TEN has a predilection for specific areas of the body. | **0.29** | 8 |
| SJS/TEN almost always affects the head and neck. | **0.16** | 7 |
| SJS/TEN almost always affects the chest. | **0.34** | 7 |
| SJS/TEN almost always affects the upper back. | **0.37** | 7 |
| SJS/TEN almost always affects the oral mucosa. | **0.13** | 8 |
| SJS/TEN almost always affects the ocular mucosa. | **0.34** | 7 |
| Blanching erythema usually can be differentiated from other cutaneous morphologies seen in SJS/TEN. | **0.60** | 7 |
| Dusky/fixed erythema usually can be differentiated from other morphologies in SJS/TEN. | **0.16** | 8 |
| Targetoid erythema usually can be differentiated from other morphologies in SJS/TEN. | **0.04** | 8 |
| Atypical targetoid erythema usually can be differentiated from other morphologies in SJS/TEN. | **0.20** | 8 |
| Vesicles and bullae usually can be differentiated from other morphologies in SJS/TEN. | **0.13** | 8 |
| Desquamation usually can be differentiated from other morphologies in SJS/TEN. | **0.29** | 8 |
| Erosions usually can be differentiated from other morphologies in SJS/TEN. | **0.13** | 8 |
| Re-epithelialized skin usually can be differentiated from other morphologies in SJS/TEN. | **0.34** | 7 |
| Mucosal bullae usually can be differentiated from other mucosal morphologies in SJS/TEN. | **0.37** | 7 |
| Mucosal erosions usually can be differentiated from other mucosal morphologies in SJS/TEN. | **0.16** | 8 |
| **Statements that the panel agreed were “inappropriate”.** | | |
| The SCORTEN is a useful tool to detect a change in skin severity. | **0.37** | 3 |
| The ABCD-10 is a useful tool to detect a change in skin severity. | **0.37** | 3 |
| Body surface area greater or less than 10% epidermal detachment is a sufficient assessment of SJS/TEN disease severity. | **0.37** | 3 |
| **Statements that the panel agreed were “uncertain”.** | | |
| The ABCD-10 should be used preferentially over the SCORTEN. | **0.52** | 4 |
| An instrument based on the “rule of 9s” is the most reliable method of estimating body surface area. | **0.52** | 6 |
| There are specific disease morphologies that can distinguish SJS from TEN. | **0.97** | 5 |
| SJS/TEN almost always affects the abdomen. | **0.52** | 6 |
| SJS/TEN almost always affects the lower back. | **0.32** | 5 |
| SJS/TEN almost always affects the anterior arms. | **0.85** | 5 |
| SJS/TEN almost always affects the posterior arms. | **0.85** | 5 |
| SJS/TEN almost always affects the anterior legs. | **0.32** | 5 |
| SJS/TEN almost always affects the posterior legs. | **0.85** | 5 |
| SJS/TEN almost always affects the palms. | **0.85** | 5 |
| SJS/TEN almost always affects the soles of the feet. | **0.45** | 5 |
| SJS/TEN almost always affects the genitalia. | **0.52** | 6 |
| SJS/TEN almost always affects the anal mucosa. | **0.32** | 5 |
| Mucosal erythema usually can be differentiated from other mucosal morphologies in SJS/TEN. | **0.52** | 6 |
| Dusky mucosal erythema usually can be differentiated from other mucosal morphologies in SJS/TEN. | **0.52** | 6 |
| Re-epithelialized mucosa usually can be differentiated from other mucosal morphologies in SJS/TEN. | **0.52** | 6 |

**Table S2.** All statements from round two

|  |  |  |
| --- | --- | --- |
|  | DI \* | Median |
| **Statements the panel agreed were “appropriate”.** | | |
| Neither the ABCD-10 nor the SCORTEN is superior to one another. | **0.65** | 7 |
| The “rule of 9s” is the most widely used method of estimating body surface area. | **0.13** | 9 |
| The “rule of 9s” is preferable to the handprint method for estimating body surface area in SJS/TEN. | **0.37** | 7 |
| SJS/TEN usually affects the abdomen. | **0.27** | 7 |
| SJS/TEN usually affects the lower back. | **0.37** | 7 |
| SJS/TEN usually affects the anterior arms. | **0.22** | 7 |
| SJS/TEN usually affect the genitalia. | **0.37** | 7 |
| Mucosal erythema that occurs in SJS/TEN cannot be reliably distinguished into severe (or dusky) or early. | **0.37** | 7 |
| **Statements the panel agreed were “uncertain”.** | | |
| SJS/TEN usually affects the posterior arms. | **0.22** | 6.5 |
| SJS/TEN usually affects the anterior legs. | **0.52** | 6 |
| SJS/TEN usually affects the posterior legs. | **0.52** | 6 |
| SJS/TEN usually affects the palms. | **0.52** | 6 |
| SJS/TEN usually affects the soles of the feet. | **0.52** | 6 |
| SJS/TEN usually affects the anal mucosa. | **0.32** | 5 |
| Mucosal erythema that occurs in SJS/TEN can be reliably distinguished from other mucosal morphologies including vesicles, blisters, and erosions. | **0.47** | 6.5 |

\* *A disagreement index value greater than 1 indicates a lack of consensus; below 1 indicates a consensus.*