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Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Standard Reporting and Evaluation Guidelines

Results of a National Institutes of Health Working Group

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IMPORTANCE Toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) are rare, acute, life-threatening dermatologic disorders involving the skin and mucous membranes. Research into these conditions is hampered by a lack of standardization of case reporting and data collection.

OBJECTIVE To establish a standardized case report form to facilitate comparisons and maintain data quality based on an international panel of SJS/TEN experts who performed a Delphi consensus-building exercise.

EVIDENCE REVIEW The elements presented for committee scrutiny were adapted from previous case report forms and from PubMed literature searches of highly cited manuscripts pertaining to SJS/TEN. The expert opinions and experience of the members of the consensus group were included in the discussion.

FINDINGS Overall, 21 out of 29 experts who were invited to participate in the online Delphi exercise agreed to participate. Surveys at each stage were administered via an online survery software tool. For the first 2 Delphi rounds, results were analyzed using the Interpercentile Range Adjusted for Symmetry method and statements that passed consensus formulated a new case report form. For the third Delphi round, the case report form was presented to the committee, who agreed that it was "appropriate and useful" for documenting cases of SJS/TEN, making it more reliable and valuable for future research endeavors.

CONCLUSIONS AND RELEVANCE With the consensus of international experts, a case report form for SJS/TEN has been created to help standardize the collection of patient information in future studies and the documentation of individual cases.

Supplemental content

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Toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) are acute life-threatening dermatologic disorders that involve the skin and mucous membranes and arise mostly from severe adverse drug reactions. These conditions are characterized by epidermal necrosis, leading to erosions of the mucous membranes, widespread detachment of the epidermis, and severe constitutional symptoms.[1,2] The incidence of TEN is estimated at 0.4 to 1.2 cases per million person-years, while SJS is estimated at 1.0 to 6.0 cases per million person-years.[3] Although rare, these disorders are associated with high morbidity and mortality even in previously healthy patients.[4]

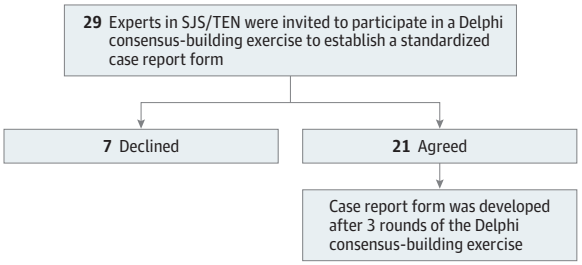
Some view TEN and SJS as variants of the same disease that differ in the extent of skin detachment, with SJS defined as having less than 10% body surface area involvement and TEN defined as involvement of more than 30% of body surface area. For the purposes of this discussion, the term "SJS/TEN" refers to the spectrum of epidermal necrolysis disorders.

More than 100 drugs have been implicated in causing SJS/TEN.[5-8] While drugs are important causes of both SJS/TEN, infectious etiologies (or a combination of infections and drugs) and malignancy-related causes have also been implicated in SJS.[9,10] In fact, SJS is idiopathic in 25% to 50% of cases.[11] Genetic susceptibility also plays a role in SJS/TEN, as evidenced by the identification of specific drug-associated human leukocyte antigen (HLA) alleles.[12-14] In addition, the pathophysiology of SJS/TEN is not well established, but the release of granulysin by cytotoxic lymphocytes and natural killer cells is thought to play a central role.[12,15] Recent studies linking HLA to drug-induced SJS/TEN have also highlighted the importance of T cells.[16-22] These seminal discoveries were made possible by carefully documented cases of TEN. Even so, there is no universally accepted standardized case report form for harmonized international reporting of TEN, the creation of which was one goal of this National Institutes of Health (NIH) SJS/TEN working group.

General guidelines for the diagnosis of SJS/TEN are typically based on the morphology and extent of the lesions in the setting of antecedent drug exposure or illness. Scoring systems have been used to assess the mortality risk in these patients, including the severity-of-illness score of toxic epidermal necrolysis (SCORTEN) scale.[23] However, due in part to the rarity of the condition, diagnostic criteria have not yet been established, which contributes to the challenge of performing high-quality retrospective studies on these patients.

For these and other reasons, there is a paucity of valuable clinical studies on SJS/TEN. In 2015, the NIH and the Food and Drug Administration (FDA) organized a workshop entitled "Research Directions in Genetically-Mediated Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis" (https://www.genome.gov/27560487) that was attended by an international panel of SJS/TEN experts. To advance the field, one of the immediate next steps identified was comparing and harmonizing case report forms and phenotyping forms. Uniform case report forms standardize the collection of patient information in a clinical study, which play a significant role in maintaining data quality. Similarly, high-quality standardized information is necessary to interpret individual case reports. Herein we present a validated case report form created from the results of a Delphi exercise performed by an NIH Working Group of participants from the 2014 NIH/FDA Workshop.

Figure. SJS/TEN Delphi Exercise Participants



Overall, 29 international experts on Stevens-Johnson syndrome and toxic epidermal necrolysis (SJS/TEN) were invited, and 21 agreed to participate.

Methods

Panel Selection

A panel of epidermal necrolysis experts (dermatologists, pharmacologists, and immunologists) from 16 different institutes and 7 different countries was assembled for a Delphi exercise to establish a standardized SJS/TEN case report form. Twenty-nine experts were identified from the NIH/FDA workshop and received email invitations to participate in the Delphi consensus-building exercise. Seven individuals did not respond, 1 declined, and the remaining 21 agreed to participate (**Figure**).

First Round

Participants were asked to evaluate the level of appropriateness of 62 statements in relation to SJS/TEN using a scale of 1 (extremely inappropriate) to 9 (extremely appropriate). The elements presented were adapted from previous case report forms and PubMed literature searches of highly cited manuscripts on SJS/TEN. They included information about pathophysiology, risk factors, patient history, signs and symptoms, diagnosis, treatment and outcome. Participants had the option of selecting "N/A" (not applicable) if they did not feel that they had the necessary expertise or background knowledge to rank a particular statement.

Surveys were administered online via SurveyMonkey and results were deidentified prior to releasing them to participants. Participants could also submit comments to be incorporated into subsequent Delphi rounds.

Statistics

Using the RAND/UCLA Appropriateness Method,[24] each item was evaluated by the 1-to-9 appropriateness rating scale and by the level of disagreement. A median appropriateness value of 1.0 to 3.4 was considered "inappropriate;" 3.5 to 6.9, "uncertain;" and 7.0 to 9.0, "appropriate." A disagreement index (DI) was calculated as described in eAppendix 1 in the Supplement. A DI value greater than 1 indicated a lack of consensus among the participants in regards to the appropriateness of the statement.

Second Round

In the second round, participants ranked new statements suggested by the panel and revised versions of the statements that failed the first round.

Third Round

Statements that were agreed upon (DI < 1) to be "appropriate" (median rating, ≥7.0) were used to develop a new set of case report forms for SJS/TEN (eAppendix 2 in the Supplement). A final version was presented to the panel for rating the appropriateness and usefulness of the newly proposed case report forms.

Results

Participant Responses

All 21 participants responded to the first Delphi questionnaire (100% response rate), and 16 of 21 participated in the second (76% response rate). The results of the first 2 rounds are presented in the Table.

For the third Delphi round, a set of case report forms was created using the approved statements and the panel "agreed" (DI = 0.31) that the forms were "very appropriate/very useful" (median value, 7). The response rate for the final exercise was 71% (15 of 21 participants).

Case Report Form

After the first round of the Delphi exercise, the panel agreed on the following items. First, SJS and TEN are a single disease with common causes and mechanism and require epidermal detachment for diagnosis. The key difference between the 2 is the extent of epidermal detachment. Second, despite having similar mucosal erosions, erythema multiforme major (EMM) and SJS are 2 distinct diseases with different patterns of cutaneous lesions. Third, the most reliable method to classify EMM, SJS, and TEN is based on the morphology and extent of epidermal detachment. Finally, mucous membrane erosions are present in all patients with SJS/TEN.

Clinical features such as morphology of the lesions, a positive Nikolsky sign, and constitutional symptoms were deemed helpful in the diagnosis of SJS/TEN. Calculating a SCORTEN was also deemed helpful. There was agreement that all patients diagnosed with SJS or TEN should receive urologic evaluation and inpatient OB/GYN screening and outpatient follow-up for female patients. All patients should also receive outpatient ophthalmology follow-up and pulmonary follow-up if there is evidence of pulmonary involvement.

The second round revealed agreements on the work-up, management, and prevention of SJS and TEN. In particular, prior to starting allopurinol or carbamazepine in a patient of Chinese descent or of other genetically at-risk populations, *HLA-B*58:01* and *HLA-B*15:02* testing should be considered, respectively. There was strong agreement that while patients with TEN should be managed in a specialized intensive care unit or burn unit, there is insufficient evidence that any specific treatment aside from supportive care is beneficial for patients with TEN.

Using the statements that the panelists "agreed" were "appropriate" in regards to SJS/TEN, a new case report form was developed. For the third and final Delphi round, the committee came to an agreement that the proposed case report form was "appropriate and useful" for documenting cases of SJS/TEN, making it more reliable and valuable for future research endeavors.

Table. Disagreement Indices for Each Proposed Item

Item	Disagreement Index
Items the panel agreed were "appropriate" for the diagnosis of TEN	
SJS and TEN are a single disease with common causes and mechanisms. The principal difference between SJS and TEN is the extent of epidermal detachment, which is limited in SJS and more widespread in TEN.	0.44
SJS and TEN are most frequently caused by drugs	0.09
SJS and TEN may be caused by infectious triggers.	0.37
SJS and TEN may be idiopathic in some cases.	0.16
Drugs discontinued more than 1 month prior to onset of mucocutaneous physical findings are highly unlikely to cause SJS and TEN.	0.13
Drugs administered longer than 8 weeks prior to the onset of mucocutaneous physical findings are highly unlikely to cause SJS and TEN.	0.65
SJS and TEN most often begin between 4 and 28 days after culprit drug administration.	0.13
Drugs highly associated with SJS and TEN include nevirapine, lamotrigine, carbamazepine, phenytoin, phenobarbital, allopurinol, anti-infective sulfonamides, oxicam-NSAIDs, and sulfasalazine.	<0.01
Valproic acid alone is not a major risk factor for the development of SJS and TEN.	0.48
Sulfonamide-related diuretics and antidiabetics are not major risk factors for the development of SJS and TEN	0.82
Acetaminophen (paracetamol) has a low associated risk for the development of SJS and TEN.	0.16
β-blockers, ACE inhibitors, calcium channel blockers, thiazide diuretics, furosemide, sulfonylurea antidiabetics, insulin, and propionic acid NSAIDs are probably not associated with SJS and TEN.	0.92
SCORTEN accurately predicts the risk of death in patients with SJS and TEN.	0.22
It is helpful to calculate a SCORTEN within the first 3 days of hospitalization.	0.16
It is helpful to use the ALDEN, an algorithm used to assess drug causality, for all patients suspected of having SJS or TEN.	0.16
It is essential to obtain detailed information on ethnicity in all patients suspected of having SJS or TEN.	0.68
It is essential to take a medication history in all patients suspected of having SJS and TEN.	<0.01
It is essential to take a medical history in all patients suspected of having SJS and TEN.	<0.01
Patients with SJS or TEN caused by a drug have a better prognosis the earlier the causative drug is withdrawn.	0.13
SJS and TEN are often heralded by fever, sore throat, cough, and burning eyes for 1 to 3 days.	0.19
Patients with SJS and TEN frequently experience burning pain of their skin at the start of disease.	0.24
Characterization of lesion morphology is helpful in the diagnosis of EMM, SJS, and TEN.	0.13
The most reliable method to classify EM, SJS, and TEN is based on lesion morphology and extent of epidermal detachment.	0.13
Classification of SJS and TEN should be based on percent of epidermal detachment alone.	0.79
Classification of SJS and TEN should be based on the nature of discrete lesions and percent of epidermal detachment.	0.16
Documentation of body surface area of baseline skin erythema is essential in all patients suspected of having SJS and TEN.	0.19
A positive Nikolsky sign is helpful in the diagnosis of SJS and TEN.	0.33
Obtaining baseline photographs of all patients suspected of having SJS and TEN is essential.	0.65
Obtaining baseline photographs of all patients suspected of having SJS and TEN is helpful but not essential.	0.29

(continued)

Table. Disagreement Indices for Each Proposed Item (continued)

Item	Disagreement Index
Typical target lesions are not present in SJS or TEN.	0.08
In the presence of epidermal detachment, atypical target lesions and macules with or without blisters are not required to diagnose TEN.	0.29
Mucous membrane erosions are present in all patients with SJS and TEN.	0.98
The epithelium of the trachea, bronchi, or gastrointestinal tract may be involved in SJS and TEN.	<0.01
Involvement of the trachea, bronchi, or gastrointestinal tract in SJS and TEN increases morbidity.	0.13
Epidermal detachment is required for a diagnosis of TEN.	0.05
A skin biopsy is helpful, but not required, to establish a diagnosis of SJS and TEN.	0.19
A skin biopsy for direct immunofluorescence is helpful, but not essential, in the evaluation of SJS and TEN	0.79
Establishment of a diagnosis of SJS and TEN by a dermatologist is helpful but not essential.	0.19
Regardless of presenting symptoms, all female patients diagnosed with SJS or TEN should receive OB/GYN inpatient screening and offered outpatient follow-up.	0.71
Regardless of presenting symptoms, all patients diagnosed with SJS/TEN should receive ophthalmology inpatient screening and offered outpatient follow-up.	0.05
It is helpful for patients diagnosed with SJS or TEN to receive outpatient ophthalmology follow-up regardless of the presence of ocular symptoms.	0.29
It is helpful for all patients diagnosed with SJS or TEN to receive urologic evaluation.	0.67
It is helpful for all patients with SJS or TEN demonstrating evidence of pulmonary involvement to receive outpatient pulmonary follow-up.	0.29
Mucosal lesions of SJS and TEN can heal with scar formation and adhesions.	0.13
Late ocular complications may develop in patients with SJS and TEN whether or not severe initial eye involvement is noted.	0.19
Restrictive lung disease may develop in patients with SJS and TEN after initial acute pulmonary involvement.	0.13
Esophageal strictures or adhesions may develop in patients with SJS and TEN after initial acute esophageal involvement.	0.29
Drugs administered 24 hours or less prior to the onset of mucocutaneous physical findings are unlikely to cause TEN.	0.13
Slow titration of a drug does not decrease the risk of it causing TEN.	0.32
Patients with TEN may experience pruritus of their skin at the start of disease.	0.26
Skin lesions of TEN usually start to re-epithelialize within 14 days and may heal without scarring. Patients may develop temporary postinflammatory hyperpigmentation.	0.19
In a patient with TEN, a Nikolsky sign may be elicited on erythematous areas of skin but may not be reliably elicited on normal appearing skin.	<0.01
It is essential to obtain an adverse drug reaction history (both for patient and family) in all patients suspected of having TEN.	0.13
In patients younger than 50 years, those who develop TEN without a suspected drug should be tested for mycoplasma pneumoniae.	0.63
Prior to starting allopurinol in a patient of Chinese descent, *HLA-B*58:01* testing should be considered.	0.13
Prior to starting carbamazepine in a patient of Chinese descent, *HLA-B*15:02* testing should be considered.	<0.01
When possible, patients with TEN should be managed in a specialized intensive care unit or burn unit.	<0.01
There is no sufficient evidence to date that any specific treatment aside from supportive care is beneficial for patients with TEN.	<0.01

(continued)

Table. Disagreement Indices for Each Proposed Item (continued)

Item	Disagreement Index
A complete blood count and comprehensive metabolic panel is helpful in evaluating patients suspected of having TEN.	0.40
Items the panel agreed were "appropriate" for the diagnosis of TEN	
Examination of all mucosal sites is essential for patients suspected of having TEN.	<0.01
Evaluation for associated symptoms is essential for patients suspected of having TEN.	0.19
The severity and risk of development of SJS and TEN does not change with a leadin or slow titration period of drugs highly associated with SJS and TEN.	0.95
Each factor calculated in the SCORTEN carries equal prognostic weight.	0.65
It is helpful but not essential to obtain detailed information on ethnicity in all patients suspected of having SJS or TEN.	0.52
Patients with SJS and TEN frequently experience pruritus of their skin at the start of disease.	0.97
Establishment of a diagnosis of SJS and TEN by a dermatologist is essential.	0.37
The presence of lymphadenopathy is helpful in evaluating a patient with TEN.	0.65
Assessing for viral reactivation (eg, herpes simplex virus) is helpful in evaluating a patient with TEN.	0.53
Items the panel agreed were "inappropriate" for the diagnosis of TEN	
SJS and TEN are exclusively caused by drugs	0.75
A skin biopsy is required to establish a diagnosis of SJS and TEN.	0.42
A skin biopsy for direct immunofluorescence is essential in the evaluation of SJS and TEN.	0.72
Items the panel disagreed on for the diagnosis of TEN	
EMM, but not SJS/TEN, can be caused by infectious triggers such as mycoplasma pneumoniae and Herpes simplex.	1.04
Drugs administered for less than 2 days prior to the onset of mucocutaneous physical findings are highly unlikely to cause SJS and TEN.	1.27
A Nikolsky sign may be elicited on erythematous areas of skin, but usually not on normal-appearing skin, in patients with SJS and TEN.	1.70
There is no correlation between the extent of epidermal detachment and mucosal membrane erosion severity in SJS and TEN.	1.46
Skin lesions of SJS and TEN usually heal rapidly without scar formation.	1.04
Factors calculated in the SCORTEN do not carry equal prognostic weight.	1.01

Abbreviations: ACE, angiotensin-converting-enzyme; EM, erythema multiforme; EMM, erythema multiforme major; NSAID, nonsteroidal anti-inflammatory drug; OB/GYN, obstetrics and gynecology; SCORTEN, severity-of-illness score for toxic epidermal necrolysis; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

Discussion

The goal of this Delphi exercise was to obtain a consensus of the elements needed to be included in a SJS/TEN standardized case report form. During each round, individuals were uniformly encouraged to give commentary on how to improve the statements or the case report form. Importantly, minority opinions that did not make the final result include adding a more detailed or complete HLA analysis and soliciting a baseline psychological history. Expanding the HLA analysis was decided against because of the low prevalence of other known mutations.

We have included various tools within the case report form such as the SCORTEN. We have not included a specific causality assessment tool because many different tools are available, but none have been shown to be superior. As part of this NIH working group, a future endeavor is to compare drug causality assessment tools, such as the ALDEN (algorithm of drug causality for epidermal necrolysis) and Naranjo.[25] Regardless of which tool is used, it is important to document who completed the causality assessment because the experience of the user can be a critical determinant of reliability.

Conclusions

We have generated, with the consensus of experts from around the world, a case report form that is the first of its kind that we know of for SJS/TEN. We are hopeful that it will help in standardizing the collection of patient information in future studies and in the reporting of individual cases of marketed drugs, leading to improved characterization and management of SJS/TEN.

ARTICLE INFORMATION

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REFERENCES

1. Lyell A. Toxic epidermal necrolysis (the scalded skin syndrome): a reappraisal. *Br J Dermatol*. 1979;100(1):69-86.

2. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med*. 1994;331(19):1272-1285.

3. Chan HL, Stern RS, Arndt KA, et al. The incidence of erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis. A population-based study with particular reference to reactions caused by drugs among outpatients. *Arch Dermatol*. 1990;126(1):43-47.

4. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med*. 1995;333(24):1600-1607.

5. Guillaume JC, Roujeau JC, Revuz J, Penso D, Touraine R. The culprit drugs in 87 cases of toxic epidermal necrolysis (Lyell's syndrome). *Arch Dermatol*. 1987;123(9):1166-1170.

6. Correia O, Chosidow O, Saiag P, Bastuji-Garin S, Revuz J, Roujeau JC. Evolving pattern of drug-induced toxic epidermal necrolysis. *Dermatology*. 1993;186(1):32-37.

7. Roujeau JC, Guillaume JC, Fabre JP, Penso D, Fléchet ML, Girre JP. Toxic epidermal necrolysis (Lyell syndrome). Incidence and drug etiology in France, 1981-1985. *Arch Dermatol*. 1990;126(1):37-42.

8. Schöpf E, Stühmer A, Rzany B, Victor N, Zentgraf R, Kapp JF. Toxic epidermal necrolysis and Stevens-Johnson syndrome: an epidemiologic study from West Germany. *Arch Dermatol*. 1991;127(6):839-842.

9. Yetiv JZ, Bianchine JR, Owen JA Jr. Etiologic factors of the Stevens-Johnson syndrome. *South Med J*. 1980;73(5):599-602.

10. Mockenhaupt M. The current understanding of Stevens-Johnson syndrome and toxic epidermal necrolysis. *Expert Rev Clin Immunol*. 2011;7(6):803-813.

11. Tyagi S, Kumar S, Kumar A, Singla M, Singh A. Stevens-Johnson syndrome—a life threatening skin disorder: a review. *J Chem Pharm Res*. 2010;2(2):618-626.

12. Heng YK, Lee HY, Roujeau JC. Epidermal necrolysis: 60 years of errors and advances. *Br J Dermatol*. 2015;173(5):1250-1254.

13. McCormack M, Alfirevic A, Bourgeois S, et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Engl J Med*. 2011;364(12):1134-1143.

14. Chen P, Lin JJ, Lu CS, et al; Taiwan SJS Consortium. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. *N Engl J Med*. 2011;364(12):1126-1133.

15. Chung WH, Hung SI, Yang JY, et al. Granulysin is a key mediator for disseminated keratinocyte death in Stevens-Johnson syndrome and toxic epidermal necrolysis. *Nat Med*. 2008;14(12):1343-1350.

16. Wei CY, Chung WH, Huang HW, Chen YT, Hung SI. Direct interaction between HLA-B and carbamazepine activates T cells in patients with Stevens-Johnson syndrome. *J Allergy Clin Immunol*. 2012;129(6):1562-1569.e1565.

17. Ko TM, Chen YT. T-cell receptor and carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis: understanding a hypersensitivity reaction. *Expert Rev Clin Immunol*. 2012;8(5):467-477.

18. Hershfield MS, Callaghan JT, Tassaneeyakul W, et al. Clinical Pharmacogenetics Implementation Consortium guidelines for human leukocyte antigen-B genotype and allopurinol dosing. *Clin Pharmacol Ther*. 2013;93(2):153-158.

19. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet*. 2002;359(9312):1121-1122.

20. Alfirevic A, Jorgensen AL, Williamson PR, Chadwick DW, Park BK, Pirmohamed M. HLA-B locus in Caucasian patients with carbamazepine hypersensitivity. *Pharmacogenomics*. 2006;7(6):813-818.

21. Correia O, Delgado L, Ramos JP, Resende C, Torrinha JA. Cutaneous T-cell recruitment in toxic epidermal necrolysis: further evidence of CD8+ lymphocyte involvement. *Arch Dermatol*. 1993;129(4):466-468.

22. Ko TM, Chung WH, Wei CY, et al. Shared and restricted T-cell receptor use is crucial for carbamazepine-induced Stevens-Johnson syndrome. *J Allergy Clin Immunol*. 2011;128(6):1266-1276.e11.

23. Bastuji-Garin S, Fouchard N, Bertocchi M, Roujeau JC, Revuz J, Wolkenstein P. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest Dermatol*. 2000;115(2):149-153.

24. Fitch K. *The Rand/UCLA appropriateness method user's manual*. Santa Monica: Rand; 2001.

25. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245.