Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Research letter

Proposing a standardized assessment of COVID-19 vaccine-associated cutaneous reactions

To the Editor: No standardized grading scale exists for the full spectrum of COVID-19 vaccine–associated cutaneous reactions, and the time cutoff of what is potentially attributable to vaccination is unclear. Skin reactions to prior vaccines have been characterized by severity scales that generally do not specify cutaneous reactions to the vaccines.[1,2] COVID-19 vaccine clinical trials used the US Food and Drug Administration's (FDA's) toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials (FDA toxicity scale).[3] Only local injection site cutaneous reactions were categorized on this scale, with little granularity to the grading of specific dermatologic conditions. This incomplete picture does not allow for the proper severity grading, assessment, and treatment of dermatology patients.

A Medline/PubMed database literature search of allergic reaction, drug reaction, and dermatologic reaction severity grading scales published from January 2000 to December 2021 was conducted for relevant literature using the following Medical Subject Headings terms: allergic reaction, severity grading scales, drug reactions, and vaccine reactions. The number of citations for each scale was identified and the 10 most cited scales for each type of reaction were evaluated. The search was subsequently expanded to include relevant terminology on the basis of the initial searches; for example, "NCI Common Terminology Criteria for Adverse Events (CTCAE)," "Ring and Messmer scale," and "Toxicity grading scale for healthy adult/adolescent volunteers enrolled in preventive vaccine clinical trials" were included to encompass the most common assessment instruments used/adapted for reaction severity grading.[4] Each scale's relevancy to grading COVID-19 vaccine–associated cutaneous reactions was assessed using a standardized data extraction tool.

We reviewed 30 articles encompassing the most cited allergic reaction scales, drug reaction scales, dermatologic reaction scales, and vaccine characterization scales. Of these, the 10 most relevant scales were analyzed for consideration in the COVID-19 vaccine–associated cutaneous reaction grading process. The FDA's toxicity scale contained relevant details on local reactions but lacked details on other types of rashes seen after vaccination.[3] The Brighton Collaboration criteria, Ring and Messmer scale, and the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network criteria were appropriate for acute onset skin reactions and anaphylaxis; however, they were not useful for describing delayed or chronic cutaneous reactions seen after vaccination. The scale capable of grading the broadest spectrum of COVID-19 vaccine–associated skin reactions was the National Cancer Institute's CTCAE scale, which has been previously adapted for drug-associated cutaneous reactions. We therefore mapped known COVID-19 vaccine–associated cutaneous reactions to the FDA's Toxicity Grading Scale (local reactions) and National Cancer Institute's CTCAE scale (generalized reactions) (Tables I and II). In general, the CTCAE scale suggests that a Grade 1 reaction involves <10% body surface area, a Grade 2 reaction involves 10% to 30%

Table I. Local injection site reactions that are immediate or delayed in onset: recommendation to classify according to the US Food and Drug Administration Toxicity Grading Scale*

Local reactions†	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially life threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of nonnarcotic pain reliever >24 h or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Erythema/redness	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration and swelling	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization

*Immediate reactions are defined by the Centers for Disease Control and Prevention as reactions within less than 4 hours of vaccine administration.
†The highest grade reached in any category (pain/redness/swelling/tenderness) determines the overall grade.

Table II. Generalized reactions: recommendation to classify according to adapted National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0 criteria

Generalized reactions*	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (eg, edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self-care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated		
Urticaria†	Urticarial lesions covering <10% BSA	Urticarial lesions covering 10%-30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; requiring injectable (IV/IM/subcutaneous) therapy		
Morbilliform	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, and tightness)	Macules/papules covering 10%-30% BSA with or without symptoms (eg, pruritus, burning, and tightness); limiting instrumental ADL; rash covering >30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL		
Zoster/shingles	Localized, local intervention indicated	Local infection with moderate symptoms; oral intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated; limiting self-care ADL	Life-threatening consequences: urgent intervention indicated	Death
Vesicular‡	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Pityriasis rosea§	Macules/papules covering <10% BSA with or without symptoms (eg, pruritus, burning, tightness)	Macules/papules covering 10%-30% BSA with or without symptoms (eg, pruritus, burning, tightness); limiting instrumental ADL; rash covering >30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL		

Pernio/chilblains[‖]	Faint discoloration, no pain, intervention not indicated	Marked discoloration, mild pain, intervention not indicated	Marked discoloration, significant pain, intervention indicated		
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10%-30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Bullous disease	Asymptomatic; blisters covering <10% BSA	Blisters covering 10%-30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self-care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Erythromelalgia[¶]	Minimal skin changes or dermatitis (eg, erythema, edema) without pain	Minimal skin changes (eg, erythema, edema) with mild pain; tingling and burning sensation; limiting instrumental ADL	Minimal skin changes (eg, erythema, edema) with significant pain; severe tingling and burning sensation; limiting self-care ADL		
Filler reaction[#]	Mild	Cosmetically significant	Cosmetically significant and interfering with function		
Angioedema[**]	Asymptomatic	Symptomatic, not interfering with function	Symptomatic bronchospasm with or without urticaria; interfering with function	Life threatening	Death
Contact dermatitis[††]	Covering <10% BSA and no associated erythema or pruritus; additional medical intervention over baseline not indicated	Covering 10%-30% BSA and associated with erythema or pruritus; limiting instrumental ADL; topical or oral intervention indicated; additional medical intervention over baseline indicated	Covering >30% BSA and associated with pruritus; limiting self-care ADL; medically significant but not immediately life threatening; IV intervention indicated		
Vasculitis	Asymptomatic, intervention not indicated	Moderate symptoms, medical intervention indicated	Severe symptoms, medical intervention indicated (eg, steroids)	Life-threatening consequences; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death
Alopecia	Hair loss of <50% of normal for the individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss, but it does not require a wig or hair piece to camouflage	Hair loss of ≥50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact			

Continued

Table II. Cont'd

Generalized reactions*	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Petechiae	Few petechiae	Moderate petechiae; purpura	Generalized petechiae or purpura		
Livedo reticularis[#]	Mild	Cosmetically significant	Cosmetically significant and interfering with function		
New dermatologic condition[‡]	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences: urgent intervention indicated	Death
Flare of an existing dermatologic condition[‡]	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self-care ADL	Life-threatening consequences: urgent intervention indicated	Death

ADL, Activities of daily living; *BSA*, body surface area; *ICU*; intensive care unit; *IM*, intramuscular; *IV*, intravenous.

*Consistent with Common Terminology Criteria for Adverse Events (CTCAE) nomenclature, a semicolon indicates "or" within the description of the grade.

[†]Immediate acute urticaria <24 hours; delayed acute urticaria <6 weeks; chronic urticaria ≥6 weeks. The scale presented in the table is from CTCAE version 5.0. The CTCAE includes "topical intervention needed" under grade 1; however, in order to align more closely with Allergy and Immunology guidelines, we have removed this from our proposed grading system. Alternatively, a scale that is used by Allergy and Immunology is "The diagnosis and management of acute and chronic urticaria: 2014 update." Stage 1: monotherapy with second generation antihistamine + avoidance of triggers. Stage 2: add another second generation antihistamine or H2 antagonist or leukotriene receptor antagonist + first generation antihistamine at bedtime. Stage 3: dose advancement of potent antihistamine. Stage 4: add omalizumab, cyclosporine, anti-inflammatory, immunosuppressants, or biologics.

[‡]Not explicitly present in CTCAE version 5.0 and, therefore, this was adapted from the version 5.0 "Skin and subcutaneous tissue disorders" generalized category.

[§]Not explicitly present in CTCAE version 5.0 and, therefore, this was adapted from the version 5.0 "Maculo-papular rash" category.

[‖]Not present in CTCAE version 5.0 and, therefore, this was adapted from the version 5.0 "Lymphedema" and "Vasculitis" categories.

[¶]Not explicitly present in CTCAE version 5.0 and, therefore, this was adapted from the version 5.0 "Palmar-plantar erythrodysesthesia syndrome" category.

[#]Not explicitly present in CTCAE version 5.0 and, therefore, this was adapted from the version 3.0 "Striae" cosmetic reactions category.

**Not explicitly present in CTCAE version 5.0 and, therefore, this was adapted from the version 5.0 "Allergic Reactions" and "Bronchospasm" categories.

[††]Not explicitly present in CTCAE version 5.0 and, therefore, this was adapted from the version 5.0 "Eczema" and "Dry Skin" categories.

body surface area, and a Grade 3 reaction involves >30% body surface area. We suggest that cutaneous reactions can be attributed to the COVID-19 vaccine only if the first instance occurs within 21 days of vaccine administration to align with prior data analysis of adverse events by authors from the Centers for Disease Control and Prevention Immunization Safety Office.[5]

The adoption of standardized terminology and grading for COVID-19 vaccine—associated skin reactions will assist researchers and clinicians in better characterizing vaccine reactions and providing appropriate counseling for patients as vaccines against COVID-19 continue to be needed globally.

Rhea Singh, BS,[a,b] Rowanne Ali, BS,[a,c] Sonya Prasad, BS,[a,d] Steven T. Chen, MD, MPH, MHPEd,[a] Kimberly Blumenthal, MD, MSc,[e] and Esther E. Freeman, MD, PhD[a,f]

From the Department of Dermatology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts[a]; Virginia Commonwealth University School of Medicine, Richmond, Virginia[b]; The George Washington University School of Medicine, Washinton, DC[c]; Icahn School of Medicine, The Mount Sinai Hospital, New York City, New York[d]; Division of Allergy and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts[e]; and Medical Practice Evaluation Center, Mongan Institute, Massachusetts General Hospital, Boston, Massachusetts.[f]

Funding sources: None.

IRB approval status: Not applicable.

Key words: adverse reactions; COVID-19; dermatology; grading scale; SARS-CoV-2; severity; vaccines.

Reprints not available from the authors.

Correspondence to: Esther E. Freeman, MD, PhD, Department of Dermatology, Massachusetts General Hospital, 50 Staniford St, Boston, MA 02114

E-mail: efreeman@mgh.harvard.edu

Conflicts of interest

Dr Chen has received honoraria from Pfizer and Novartis for serving on an advisory board for digital media. Dr Freeman is a member of the American Academy of Dermatology COVID-19 Ad Hoc Task Force, is an Editor for the *British Journal of Dermatology*, and is an author of COVID-19 dermatology for UpToDate. Authors Singh, Ali, and Prasad and Dr Blumenthal have no conflicts of interest to declare.

REFERENCES

1. Popmihajlov Z, Pang L, Brown E, et al. A post hoc analysis utilizing the FDA toxicity grading scale to assess injection site adverse events following immunization with the live attenuated zoster vaccine (ZVL). *Hum Vaccin Immunother*. 2018;14(12):2916-2920.
2. Gutiérrez RL, Porter CK, Jarell A, Alcala A, Riddle MS, Turiansky GW. A grading system for local skin reactions developed for clinical trials of an intradermal and transcutaneous ETEC vaccine. *Vaccine*. 2020;38(21):3773-3779.
3. Norquist JM, Khawaja SS, Kurian C, et al. Adaptation of a previously validated vaccination report card for use in adult vaccine clinical trials to align with the 2007 FDA Toxicity Grading Scale Guidance. *Hum Vaccin Immunother*. 2012;8(9):1208-1212.
4. US Department of Health and Human Services. Common terminology criteria for adverse events (CTCAE). Version 5.0. Published November 27, 2017. Accessed January 18, 2022. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf
5. Klein NP, Lewis N, Goddard K, et al. Surveillance for adverse events after COVID-19 mRNA vaccination. *JAMA*. 2021;326(14):1390-1399.

https://doi.org/10.1016/j.jaad.2022.05.011