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United States Drug Allergy Registry (USDAR) Grading Scale for Immediate Drug Reactions

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Abstract

Background: There is no accepted grading system classifying the severity of immediate reactions to drugs.

Objective: The purpose of this article is to present a proposed grading system developed through the consensus of drug allergy experts from the United States Drug Allergy Registry (USDAR) Consortium.

Methods: The USDAR investigators sought to develop a consensus severity grading system for immediate drug reactions that is applicable to clinical care and research.

Results: The USDAR grading scale is scored on a 0 to 4 scale of severity levels. A Grade NR is used for patients who undergo challenges without any symptoms or signs and would confirm a negative challenge. A Grade 0 reaction is indicative of primarily subjective complaints that are seen commonly with both historical drug reactions and during drug challenges and would suggest a low likelihood of a true drug allergic reaction. Grades 1 to 4 meet the criteria for a positive challenge and may be considered as a drug allergy. Grade 1 reactions are suggestive of a potential immediate drug reaction with mild symptoms. Grade 2 reactions are more likely to indicate an immediate drug reaction with moderate severity. Grade 3 reactions have features to suggest a severe allergic reaction while grade 4 reactions are life-threatening reactions such as anaphylactic shock, and fatal anaphylaxis.

Conclusion: This proposed grading schema for immediate drug reactions improves on prior schema by being specifically developed for immediate drug reactions and being easy to implement in clinical and research practices.

Clinical Implications: The USDAR grading scale for immediate drug reactions is a user-friendly scale and easy to implement in clinical and research practices.

Capsule Summary:

The USDAR grading scale for immediate drug reactions improves on prior schema by being specifically developed for immediate drug reactions and being user-friendly and easy to implement in clinical and research practices.

Keywords

drug allergy; drug challenge; severity; grading; drug reaction; USDAR; consensus; immediate hypersensitivity

INTRODUCTION

Standardized reaction grading systems enable the comparison of safety outcomes associated with different diagnostic or therapeutic approaches in allergy and immunology. Although grading systems for immediate hypersensitivity reactions have been developed over the past decades, with thorough severity grading systems in allergen immunotherapy,[1–4] venom anaphylaxis,[5] and food allergy,[6–8] scales specific for use for drug allergy have neither previously been systematically implemented nor evaluated. While it has been proposed that with modification, the WAO (World Allergy Organization) classification for systemic allergic reactions can be applied to medications,[3] to date, WAO grading has not routinely been used in drug allergy. Although drug allergy is a core component of allergy and immunology practice, no allergy scale has been specifically developed with the unique challenges that drug allergy assessments present. As such, despite encouragement to use WAO and other typical allergic reaction grading scales, drug allergy investigators have used and adapted other scales to suit their needs.[5,9] (Table 1) In addition to using an ordinal severity score, studies have also used therapeutic choice of a reaction to convey severity, specifically epinephrine use for immediate reactions.[31]

The United States Drug Allergy Registry (USDAR) is a multisite, longitudinal prospective cohort designed to study drug allergy and clinical outcomes.[32]As drug allergy emerges as a diverse field that is critical to scale across the United States and globally, it has become increasingly important to build more generalizable knowledge from clinical studies. For results to be compared or compiled across settings, use of one severity scale is necessary. To address this unmet need in the field of drug allergy, the USDAR investigators sought to develop a consensus severity grading system for immediate drug reactions (not vaccines) that is applicable to clinical care and research. Immediate drug reactions are reactions that occur within 6 hours after the last drug administration.[33] The initial grading system, drafted by 2 authors (DAK and KGB), underwent multiple iterative revisions guided by comments from all co-authors until a consensus was reached.

METHODS

Rationale for Developing a Drug Allergy Specific Assessment Tool

Different grading schemes have been developed for specific types of allergic reactions, such as anaphylaxis, stinging insect hypersensitivity, immunotherapy, and food challenges. Recently, a multidisciplinary group of allergy and emergency care experts developed a

consensus severity grading system for acute allergic reactions utilizing a Delphi method.[34] In this report, several limitations of prior grading systems were noted, including difficulty with discriminating between clinically important phenotypes of reactions, non-specific terminology, use of similar terms, including subjective and objective criterion between different grades, reliance on the number of organ systems to determine severity, grading based on therapeutic intervention and symptom duration and impracticality. The severity scheme developed by this consensus group included severity grades 1–5, ranging from mild to severe. Their stated goal was to develop a generalizable grading system that could be used across a variety of clinical applications, allergens and modes of exposure.

The authors of this article agree with many of the limitations outlined. However, as experts in drug allergy clinical care and research, we do not consider that a generic severity scale will have applicability to immediate reactions associated with medications for several reasons. One important aspect of drug challenge is consideration of reactions to placebo (ie, nocebo responses).[35,36] An overview of 20 systematic reviews of nocebo effects reported by 250,726 patients taking placebos in clinical trials showed a median prevalence of adverse events of 49.1% and a median drop-out rate of 5%.[37] Drug allergy testing is particularly fraught with a high frequency of patients reporting subjective symptoms that are not consistent with allergy, especially during observed drug challenges. For example, among 123 patients challenged to drugs at 1 institution, there were 102 with no symptoms, 20 with subjective symptoms, and 1 who had an allergic reaction.[38].) In a study of 228 patients undergoing drug challenges, 137 (60%) experienced nocebo reactions.[35] While 71.5% of these reactions were subjective (most commonly pruritus without rash), objective findings occurred in 11.7% of patients most commonly flushing or urticarial lesions. A patient with both nausea and pruritus would inappropriately score a 2 on the recently proposed Delphi-based severity grading scale.[34] Subjective complaints are common with drug challenges[38] and the most recent updated Drug Allergy practice parameter indicates that subjective symptoms alone would not confirm drug allergy.[39] Since antibiotics are one of the most common drugs tested, gastrointestinal symptoms such as abdominal pain and nausea are well-known adverse effects that could be potentially confused for an allergic reaction.

RESULTS

Attributes of a Drug Reaction Grading System

The authors of this article determined that a grading system for drug reactions would ideally be applicable for both grading of historical reactions to drugs, as well as being used for drug challenge procedures. Retrospective determination is critical to determine if the reported symptoms and/or signs are consistent with an allergic reaction and/or are supported by objective findings. Drug reaction severity scales should also not overly rely on the latency, or time course of symptoms. Since drugs may be administered by different routes, these differences may impact the onset of allergic reactions. Grading schemes have been reliant in the past on strict times, including how reaction timing can impact severity using this score, with more rapid onset reactions receiving higher grades. Reaction timing was also used by the European Academy of Allergy and Clinical Immunology task force; urticaria was a different grade depending on when it presented (grade II if >15 min and grade III is <15

min[40]). Such timing does not specifically account for drug reactions that occur via challenge through different routes such as parenteral, intramuscular, or oral.

Gastrointestinal symptoms are routinely included in universal grading schemes. However, isolated gastrointestinal symptoms are not considered manifestations of an allergic reaction to a drug, however gastrointestinal symptoms as a manifestation of multi-organ drug-induced anaphylaxis have been well described[41, 42] to a variety of medications. Furthermore, many medications have gastrointestinal symptoms as their most common adverse effect. This is certainly true with antibiotics which are the most frequent drugs administered during drug challenges. For these reasons, the authors determined that the use of gastrointestinal symptoms without other findings had little value in determining severity of drug reactions. While patients with aspirin exacerbated respiratory disease may have isolated gastrointestinal symptoms during aspirin desensitization, this scale is not intended for use during desensitization procedures. Whether the addition of gastrointestinal symptoms to other symptoms (e.g., hives and abdominal pain vs. hives alone) would change severity and outcomes will require further study. Laryngeal symptoms, particularly symptoms of throat tightness are commonly reported by patients with histories of drug reactions and are also observed during drug challenges. However, isolated laryngeal symptoms due to laryngeal edema are exceedingly uncommon. Inducible laryngeal obstruction (e.g., vocal cord dysfunction), which can lead to symptoms as well as signs such as stridor which are non-allergic in nature have been well documented to occur with drug challenges.[41,42].

Although consideration of pharmacologic treatment is included in some grading systems, and has been used generally to convey reaction severity, this information may be inconsistently available or not representative of the true reaction. As acknowledged by others, the decision to administer epinephrine (or not) is inconsistent across clinicians, patients and even geographic regions. Patient factors (including patient anxiety) may be used to justify reaction treatment when there may not have been an allergic reaction at all. For these reasons we did not include epinephrine treatment in a scale for drug allergy.[34]

The USDAR Grading Scale for Immediate Drug Reactions

The USDAR grading scale was designed to be a straightforward scale that does not require cross-referencing other scales or complex calculations (Table 2). Its main purpose is to grade immediate reactions with drug challenges, but it also has the potential to be used to grade historical drug reactions which are commonly encountered in clinical practice, as this could be used for consistent risk calculations. The USDAR grading scale is scored on a 0 to 4 scale of severity levels. A Grade NR (no Reaction) is used for patients who undergo challenges without any symptoms or signs and would confirm a negative challenge. A Grade 0 reaction is indicative of primarily subjective complaints that are seen commonly with both historical drug reactions and during drug challenges. This severity score would suggest a low likelihood of a true drug allergic reaction, and for a drug challenge, would not meet criteria for a positive challenge or confirmed allergy. Grades 1 to 4 meet the criteria for a positive challenge result and may be considered a drug allergy, Grade 1 reactions are suggestive of a potential immediate drug reaction with mild symptoms. Grade 2 reactions are more likely to indicate an immediate drug reaction with moderate severity. Grade 3 reactions have features

to suggest a severe allergic reaction while grade 4 reactions are life-threatening reactions such as anaphylactic shock, and fatal anaphylaxis.

For mucocutaneous features, the use of a quantifiable number of hives was thought to provide more objective and clear criteria. The threshold of ≥ 5 hive lesions to differentiate grade 1 and grade 2 reactions, while consistent with clinical expertise, is arbitrary and will require further study to determine its validity. While our group considered the use of body surface area (BSA) measurement, the authors felt that, in clinical practice, many allergy clinicians are less familiar with calculation of BSA generally leading to overestimation, and this could lead to greater error or limit the use of this tool clinically. Furthermore, calculation of BSA involvement for historical reactions would be problematic but the number of hives may be recalled. For severity of respiratory reactions, the use of oxygen saturation was felt to be the best discriminator for the severity of reactions given the large overlap between subjective symptoms that could be anxiety related versus true immediate allergic drug reactions. However, there are many pitfalls to the use of pulse oximetry including the proposed ranges identified and requirement for baseline SpO2 ≥ 97%. Additional well-documented pitfalls of pulse oximetry which can lead to falsely high or low readings include errors due to motion artifact, racial disparities from skin pigmentation, nail polish, vascular perfusion, breath-holding, variability in accuracy between oximetry devices and others.[45–47] Despite this, pulse oximetry will likely prove helpful for drug challenges, but the absence of a reading may under-estimate the severity of a historical reaction and this will require further analysis in validation studies. For cardiovascular reactions, the definition for moderate to severe hypotension is consistent with that used by prior anaphylaxis symposia criteria[48] and the recent report using the Delphi methodology.[34] As explained, and as opposed to most other allergic grading systems, the authors determined to exclude gastrointestinal features from this severity scale. In addition, neurologic features were also excluded as isolated, neurologic symptoms without other respiratory or cardiovascular features would be a very unusual manifestation of an immediate allergic drug reaction.

For immediate drug challenges, the typical observation period is 30–60 minutes.[39] Thus, reactions can be graded during this period of direct observation. Grading reactions that occur up to 6 hours later will be a challenge as objective findings will not be available, and most reactions will thus be self-reported. Photo documentation of any rash or swelling that develops after an observation period should be encouraged. Further studies will need to determine the utility of this scale for such self-reported reactions.

DISCUSSION

Like all other grading systems developed for allergic reactions by expert opinion, this grading system requires validation. Future studies will include internal and external validation studies and usability testing across our multi-site collaboration. The criteria used to differentiate severity levels based on the time from last dose, number of hives, pulse oximetry level, and blood pressure changes require further validation in clinical studies that will capture these physiologic assessments as continuous variables for refinement. It is expected that with further use and experience and validation studies, modifications to this system will likely occur. This plan for grading immediate reactions to drugs is

analogous to the Consortium of Food Allergy Research (CoFAR) grading scale used for food induced systemic allergic reactions, which was initially used in clinical trials prior to validation.[44] With subsequent use and more experience, modifications to the CoFAR grading scale have been proposed.[45] The USDAR Consortium hopes to utilize this grading system in future clinical studies and will plan to validate this system and make adjustments, as indicated. While consensus methods can include Delphi methodology, this was not used in this stage of development as there was broad consensus on this initial version of the USDAR grading system by the primary investigators in the group. This grading system is specifically designed for adults with histories of immediate reactions to medications and does not apply to reactions to vaccines or non-immediate reactions, including severe cutaneous adverse drug reactions. In addition, the intention of this scale is for use with drug challenges and additional studies are needed to determine its utility to assess historical reactions. Furthermore, this severity scale is not intended to be used to guide allergic reaction treatment and additional studies would be required to determine if this severity scale would be useful to predict future reactions to drug exposure.

Conclusion

We believe that this proposed grading schema for immediate drug reactions improves on prior schema by being specifically developed for immediate drug reactions and being user-friendly and easy to implement in clinical and research practices. We believe that consistent use of a unified grading system will be critical to objectify severity in the clinical and research settings and decrease variability in reported outcomes site to site to facilitate combining studies and protocols through multi-site clinical research as well as meta-analytic approaches.

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Abbreviations:

WAO	World Allergy Organization
USDAR	United States Drug Allergy Registry
NR	no reaction
BSA	body surface area
CoFAR	Consortium of Food Allergy Research

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Table 1.

Select Drug Allergy Studies Reporting Reaction Grades

Modified From	Grades and Definitions	Drug Allergy Domain and References
Ring and Messmer(9)	Grade I, Skin symptoms and/or mild fever reaction Grade II, Measurable, but not life-threatening; cardiovascular reaction (tachycardia, hypotension); gastrointestinal disturbance (nausea); respiratory disturbance Grade III, Shock, life-threatening spasm of smooth muscles (bronchi, uterus) Grade IV, Cardiac and/or respiratory arrest	Perioperative allergic reactions(10–13) Chemotherapy and biologic reactions/desensitization reactions(14, 15)
Brown(5)	Grade 1, Mild symptoms are limited to the skin (e.g., flushing, generalized erythema, urticaria, periorbital edema, or angioedema) or involve a single organ/system and are mild (e.g., mild back pain) Grade 2, Moderate symptoms involve at least 2 organs/systems (e.g., flushing and dyspnea), but there is no significant decrease in blood pressure or oxygen saturation Grade 3, Severe symptoms typically involve at least 2 organs/systems, and there is a significant decrease in blood pressure (systolic <90 mm Hg and/or syncope) and/or oxygen saturation (<92%), confusion, collapse, or loss of consciousness or continence.	Chemotherapy and biologic reactions/desensitization reactions(16–19)
Sixth National Audit Project (NAP6) severity of perioperative hypersensitivity reactions(20)	Grade 1, Rash, erythema, swelling (any of) Grade 2, Unexpected hypotension-not severe, bronchospasm-not severe, or both ± grade 1 features Grade 3, Unexpected severe hypotension ±severe bronchospasm, ±swelling with actual of potential airway compromise, ±grade 1 features Grade 4, Fulfilling indications for cardiopulmonary resuscitation Grade 5, Death	Perioperative allergic reactions(21–25)
National Cancer Institute(26)	Grade 1A, Cutaneous rash, flushing, generalized pruritus Grade 1B, 1A Signs and symptoms with back pain or hypertension Grade 2, Urticaria, nausea/vomiting, throat tightness, asymptomatic bronchospasm, chest tightness Grade 3, Symptomatic bronchospasm, dyspnea, hypoxia, wheezing Grade 4, Anaphylaxis, hypotension Grade 5, Death	Chemotherapy and biologic reactions/desensitizations(17, 27–30)

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Table 2.

USDAR Grading Scale for Immediate Drug Reactions

Grading Severity	Grade NR^	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
*Reaction Criteria	No symptoms or signs	Reactions with primarily subjective symptoms only that improve/resolve without treatment to include any of the following:	Reactions with 1–2 of the following:	Reactions with ≥ 2 of the following:	Reactions with ≥1 of the following:	Reactions resulting in any of the following conditions or interventions:
Mucocutaneous Features		Pruritus without rash, tingling, subjective lip/tongue swelling	Flushing/erythema, < 5 hives, angioedema of lip, face, or eyelid	≥ 5 hives, documented tongue or soft palate/uvula edema	Tongue or uvula edema with dysphonia (surrogate for laryngeal edema) or documented laryngeal edema by laryngoscopy	NA
Respiratory Features		Dyspnea, cough, tongue or throat sensation without objective changes, chest tightness	Dyspnea, cough, throat tightness, or chest tightness/discomfort with SpO2=93–94% ** or Wheezing with SpO2 ≥93%	Dyspnea, cough, throat tightness, chest tightness/ discomfort, or wheezing with oxygen desaturation (SpO2= 90–92%)	Oxygen desaturation with SpO2 < 90%	Intubation performed for respiratory failure
Cardiovascular Features		Dizziness, lightheadedness, heart racing, palpitations, tachycardia, hypertension	NA	Mild hypotension SBP > 90 mmHg and 20–29% decrease from baseline	Moderate-severe hypotension SBP < 90 mmHg and > 30% decrease from baseline ***	Pulseless Cardiopulmonary resuscitation performed Death

^ NR: No Reaction, SBP: Systolic blood pressure, SPO2: Specific oxygen saturation as measured by pulse oximetry.

* The grading severity is defined by the reaction criteria described for each column. Reactions not meeting the number of needed criteria in a given column would be graded one grade lower (e.g., 5 hives but no other symptoms = Grade 1). For reactions that meet criteria for multiple columns, the highest grade would be applied (e.g., ~50 hives [Grade 2] and a SBP of 80 mmHg with a 35% decrease from baseline [Grade 3] would be scored a Grade 3 reaction).

** Applies to baseline SpO2 ≥ 97%

*** Vasovagal reactions may result in hypotension associated with bradycardia and prompt resolution with supine position and are not consistent with a Grade 4 reaction.

NA: not applicable

Immediate reactions are defined as reactions that occur within 6 hours after the last drug administration.

Isolated gastrointestinal symptoms are not considered manifestations of an allergic reaction to a drug