As populations age, the prevalence of reported drug “allergy” increases, often leading to suboptimal care and increased morbidity because of unnecessary avoidance of safe and effective medications. Evaluation by a drug allergy specialist is often warranted when a patient has more than 2 unrelated drug “allergies” listed in the medical record. In this commentary, we clarify and propose standard terminology to use when evaluating patients with multiple drug allergy labels including and more specifically when diagnosing multiple drug intolerance syndrome and the much rarer multiple drug hypersensitivity syndrome. We review epidemiology and key features of multiple drug intolerance syndrome and multiple drug hypersensitivity syndrome. We summarize the methodologic and practical diagnostic workup and management of individuals with MDIS to assist with the accurate delabeling of drug “allergies” in the electronic health record.  © 2020 Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:2870-6)

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INTRODUCTION

In clinical practice, patients often self-report “allergies” to a number of drugs and to multiple drug classes. In any patient with a documented drug “allergy,” there is significant morbidity and mortality associated with this label.1 Because there have been a number of definitions and classification systems proposed in the medical literature for reporting and documenting drug reactions, it is nonetheless essential to adapt standard terminology when diagnosing patients with reactions to medications, which we define below. Drug “allergy” and “allergies” are used in quotation marks throughout this review to highlight that most drug reactions are not immune-mediated, and therefore not true allergies.

Adverse drug reactions (ADRs) include all unintended effects of drugs that occur because of their inherent pharmacologic properties.2 ADRs, independent of cause and other disease-associated symptoms incorrectly attributed to drug use, are frequently reported by patients and documented as “allergies” in the electronic health record (EHR), without confirmation or clarification of the mechanism. Incorrectly labeling these as “allergies” leads to confusion and to possible therapeutic disadvantages. A detailed discussion of the types of ADRs is not relevant for this review; however, a brief mention of the historical classification system of ADRs is necessary to understand our proposed standard use of definitions. ADRs have been historically classified as “type A” reactions, which are common and predictable, and “type B” reactions, which are rare and generally unpredictable. Type A reactions include side effects to drugs such as oral thrush seen with use of glucocorticoids; indirect effects of drugs as seen in diarrhea from antibiotics; and, finally, drug-drug interactions. Type B reactions have historically been referred to as hypersensitivity reactions and are primarily mediated by inflammatory and immune mechanisms. Type B reactions include intolerances, idiosyncratic reactions such as hemolytic anemia after use of drugs in a patient with G6PD deficiency, and immunologic drug reactions or drug hypersensitivity reactions (DHRs), which are defined below.3,5

A more modern approach to ADR classification has been published following advances elucidating mechanisms of ADRs, which differentiates primary on-target pharmacological effects (previously referred to as “type A” reactions) from off-target effects at distant receptors (previously referred to as “type B” reactions).6 More recent studies have demonstrated that both on-target and off-target effects may be predictable.7 DHRs are adverse reactions, and more specifically a type of off-target hypersensitivity reaction, with an established immune-mediated mechanism. DHRs account for a small number of ADRs, approximately 6% to 10%.2,5 DHRs may be immediate in onset (occurring acutely within 1 hour of the first dose of the last exposure, but by international convention up to 6 hours later) or nonimmediate in onset (occurring after 6 hours by international convention, but typically more than 24 hours after the first dose of the last exposure).2,8,9 Multiple mechanisms may trigger immediate-onset reactions that involve IgE, IgG, direct mast cell activation, and basophil activation.1,8 It is often possible to induce tolerance to a drug (ie, desensitize) in individuals with IgE-mediated allergy, which is the defining hallmark of a type 1 immediate-onset DHR.10 Non–immediate-onset DHRs may be caused by a number of non–IgE-mediated mechanisms; however, T-cell–mediated mechanisms are the most common.11

Multiple drug hypersensitivity syndrome (MDHS), formerly referred to in the literature as multiple drug allergy syndrome, is defined as allergic reactions to 2 or more unrelated drugs by immune-mediated mechanisms.10,15 In addition, there are other definitions for MDHS that describe this syndrome as 3 or more allergic reactions to unrelated drugs, to ensure there is lack of coincidental co sensitization to 2 drugs.16 Although both definitions are currently in use, patients truly allergic to 3 or more unrelated drugs likely represent a special group that should be studied further. MDHS is rarely confirmed, but when it has been confirmed, the suspected mechanism is typically T-cell–mediated hypersensitivity.17

Drug intolerances are a type of hypersensitivity reaction that includes any undesirable and non–immune-mediated effect of a drug.17 Although this type of reaction was historically classified as an unpredictable “type B” reaction, there is evidence that some intolerances may follow a more predictable pattern. Although often referred to as a drug “allergy,” these reactions mostly remain unvalidated, complicating the medical treatment for patients and leading to unnecessary avoidance of many first-line drugs for treatment.

The clinical symptoms reported by patients that include gastrointestinal symptoms or headaches are often incorrectly labeled and referred to as “allergies.” These symptoms should not be recorded in the EHR as allergies and instead as intolerances or side effects. These options are available in most EHR systems.18

Multiple drug intolerance syndrome (MDIS) is intolerance to 3 or more chemically unrelated drugs.16,19 MDIS is not immune-mediated and has no defined mechanism responsible for the adverse reactions or claimed intolerance to medications. Virtually all patients seen by allergists with multiple entries in their drug “allergy” field of the EHR have MDIS. See Figure 1.

This review will focus primarily on the patient with multiple drug allergy labels. All medical providers, especially those providers who see patients on a routine or regular basis, should be encouraged to identify and remove inappropriate and incorrect “allergies” in the EHR, because minimal training is required for the recognition and identification of predictable, nonimmune on-target ADRs, previously referred to as “type A” reactions. However, patients with a history of multiple drug “allergies” or those with an unclear clinical picture should be referred to drug allergy specialists. The overall aim of this commentary was to assist the drug allergy specialist with a practical approach to phenotype, manage, and remove drug “allergies” from individuals with multiple drug allergy labels.

EPIDEMIOLOGY

Most prevalence data on MDIS and MDHS come from adult studies. The prevalence of MDIS in adults has been estimated to be between 2% and 6%.10,19 Macy and Ho16 reported on the
population-based prevalence of MDIS in children, which made up 1.4% of their moderate MDIS cohort (defined as 3 or more different drug class “allergies”) and only 0.2% of their severe MDIS cohort (defined as 4 or more different drug class “allergies” with 10 or more unique medication entries in the drug “allergy” fields). Confirmed MDHS is much less frequent. A recent publication found the prevalence of MDHS to be 1%, compared with 6% in MDIS. Although the overall prevalence of MDIS is lower than the prevalence of other allergic and immunologic conditions, there is great complexity involved in the overall evaluation, diagnosis, and management of MDIS. Unfortunately, there is a paucity of literature on this topic. Therefore, it is not surprising that physicians who care for patients with a long list of drug “allergies” listed in the EHR avoid these medications out of fear and uncertainty of eliciting possible severe reactions, which may ultimately lead to use of potentially less effective and sometimes more toxic drug treatments.

Both MDIS and MDHS have been reported to multiple drug classes. Common culprits identified in a recent large study include beta-lactams and sulfonamide antibiotics, antiepileptics, hypnotics, antidepressants, local anesthetics, glucocorticoids, opioids, and nonsteroidal anti-inflammatory drugs (NSAIDs). The primary risk factors for MDIS are female sex, increasing age, higher rates of medication exposures, previous hospitalizations, nonlethal comorbidities (especially hypertension), depression, and anxiety. An individual with any drug “allergy” is more likely to report a new drug “allergy” with every medication exposure than a matched individual with no reported drug “allergy.” Female sex and intolerance to NSAIDs was identified as a risk factor for MDHS.

It should come as no surprise that the clinical presentation of MDIS varies broadly, given the lack of a known immunologic mechanism, from rashes to gastrointestinal complaints and other nonspecific subjective complaints. Cases of MDHS, although rare, have reported severe cutaneous reactions such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, also called drug-induced hypersensitivity syndrome.

It is nonetheless essential for clinicians to accurately document drug reactions and use the proposed standard definitions in EHRs to avoid misclassification as “allergies” and to support future epidemiologic studies.

**INITIAL EVALUATION**

A complete clinical history is the key to evaluating risk in individuals who report multiple drug “allergies.” The factors most likely to be associated with immediate-onset hypersensitivity, specifically IgE-mediated allergy, are the time from the first dose of the last exposure (typically <1 hour) and the nature of symptoms, specifically urticaria, angioedema, respiratory distress, presyncope/syncope, and/or anaphylaxis. Most individuals who are given an International Classification of Diseases, Ninth Revision or International Classification of Diseases, Tenth Revision diagnosis code of anaphylaxis after exposure to a penicillin or a cephalosporin do not meet the clinical criteria for a diagnosis of anaphylaxis after chart audit.

Nonimmediate or delayed DHRs, specifically T-cell–mediated hypersensitivity, could manifest as a maculopapular eruption starting after 2 to 5 days and several weeks after the first dose of the medication has been started. The more feared, and potentially lethal, severe cutaneous adverse reactions can begin up to several weeks after starting a drug. SJS, defined as less than 10% body surface area desquamation, is typically overdiagnosed. TEN, defined as greater than 30% body surface area desquamation, and SJS-TEN overlap, which involves 10% to 30% body surface area desquamation, are typically coded more accurately in EHRs. Therefore, careful documentation of the reaction with photographs from the patient and the timeline of the disease course is of utmost importance.

A detailed review of the health record to assess for objective signs of reaction, including documentation of hypotension and/or hypoxemia and review of laboratory results (eg, eosinophil count, liver function tests, creatinine, and tryptase), should be performed.

It is highly informative to inquire with the patient or caregivers about the treatment that the patient has received for the reported reaction. Treatment intensity (eg, oral antihistamines vs resuscitation or intubation) could be indicative of reaction severity.

Moreover, a detailed timeline of the disease course and latency will point to possible culprit drugs and guide further testing and clinical disease management.

**OBJECTIVE TESTING**

Skin testing for suspected type I, IgE-mediated DHRs, using previously published nonirritating concentrations of drugs, should be considered for some drugs, at least 2 to 4 weeks after the
reaction. Some skin testing to drugs that cause immediate-onset DHRs that are not thought to be IgE-mediated, such as opiates, NSAIDs, and quinolones, are of limited utility and not recommended. Negative skin test results do not exclude immune-mediated reactions because some patients may be hypersensitive to metabolites of the medication or metabolite/protein complexes. If skin testing result is negative, a repeated skin test could be considered at a later time point if the reaction was relatively recent (within a few weeks). Some publications suggest waiting at least 4 to 6 weeks after an anaphylactic reaction to avoid possible false-negative results from temporary loss of cutaneous mast cell reactivity, although the evidence to support delay in testing is limited and primarily based on clinical experience. In addition, a graded drug challenge or single-dose challenge may be considered on the basis of severity of the initial reaction.

When indicated, patch testing or delayed intradermal testing can be performed and may aid in the diagnosis of delayed reactions such as maculopapular exanthema, DRESS, or acute generalized exanthematous pustulosis. Drug patch testing and delayed intradermal testing are discussed in detail in an accompanying article in this theme issue.

### ROLE OF DRUG CHALLENGES IN THE EVALUATION OF DRUG INTOLERANCES AND MDIS

Patients with a suspicion for MDIS are often ideal candidates for drug challenges given their historical reactions appear unlikely to be immune-mediated. Drug challenges are performed to exclude DHRs in patients with a low likelihood of reacting to the
drug in question. Graded drug challenges involve the cautious administration of incremental doses of a medication until a therapeutic dose is reached with the intention of confirming tolerance. However, when the historical reaction is mild and the probability of reaction is low in a specific patient, a single-dose challenge could be considered. Graded challenges should not be performed in patients with a previous positive skin test result to the drug. Further contraindications to a graded drug challenge include a history of severe cutaneous adverse reactions that involved blistering dermatitis (eg, SJS or TEN), sloughing of the skin, involvement of internal organs (eg, DRESS/drug-induced hypersensitivity syndrome), and milder dermatoses with mucous membrane lesions (eg, erythema multiforme). Pregnancy and patients with increased risk due to comorbidities (uncontrolled asthma, underlying cardiac condition, or any situation in which the challenge can provoke an uncontrolled medical emergency) are relative contraindications. In such cases, the benefits of the procedure should be carefully weighed against their risks and discussed with the patients or caregivers.

The utility of graded challenges for patients with suspected MDIS was assessed in an Italian study of 480 patients who reported a history of adverse reactions to at least 3 chemically and pharmaceutically unrelated drugs. Patients first underwent a series of drug allergy tests that included skin tests, patch tests, measurement of specific and total IgE levels, and measurement of serum eosinophilic cationic protein to identify a possible immunologic etiology underlying their reactions. All study patients had negative immunologic test results. A total of 411 (70 males and 341 females) of 480 patients subsequently underwent 1882 four-step graded challenges to an alternative drug that did not belong to the same family as any of the inciting drugs. Eighty-four percent of patients with a mild initial reaction tolerated their graded challenge to an alternative drug, whereas 89% of patients with a previous history of a moderate adverse reaction tolerated their challenge after premedication with sodium cromolyn. Eighty-nine percent of patients with a history of a severe reaction who were pretreated with an antihistamine 30 minutes before the challenge tolerated the alternative drug. Although this protocol allowed for the successful introduction of alternative drugs, the initial drugs were not rechallenged.

A study by Ramam et al included 23 patients with reported historical reactions to 2 or more unrelated drugs. Only 3 of 350 subsequent drug challenges performed in a hospital setting elicited reactions, all of which were to NSAIDs. Most challenges were performed by administering a single therapeutic dose of the drug. Most patients also received placebo on the first day of their challenge and 6 patients (26%) reported symptoms. One of the major limitations of this study is that all patients were hospitalized for the sequential drug challenges and it is unknown whether patients were challenged to the drug that was reported to have caused the initial reaction or an alternative drug.

Because patients with MDIS often report subjective symptoms, it is essential that practitioners assess for objective signs and symptoms of a reaction during a drug challenge to eliminate false-positive results. The addition of a placebo to drug challenges can aid in the identification of DHRs and can be considered when initial drug challenge results are indeterminate. Iammatteo et al studied a 3-step challenge protocol in which a placebo in the form of berry-flavored yogurt mixed with cherry-flavored pharmaceutical sweetener was administered before a 2-step oral graded drug challenge (1/10th of the therapeutic dose of the drug followed by 30 minutes of observation and subsequent administration of a full therapeutic dose followed by 60 minutes of observation). The challenge drugs were also mixed in the same vehicle as the placebo. Only 10 of 229 patients (4.4%) had objective findings during drug challenges, whereas 20 patients (8.7%) reacted to placebo, all of whom were female with a baseline of 2.7 reported drug reactions. Patients with 3 or more reported drug allergies were also significantly more likely to react to placebo. Therefore, it is possible that some of these female patients had MDIS.

In a subsequent study by Iammatteo et al on the safety of placebo-controlled oral graded challenges to amoxicillin without prior skin testing in 155 patients with a history of non–life-threatening historical reactions to penicillin, only 2.6% of patients developed mild positive challenge reactions whereas 10.3% reacted to placebo. Although the addition of placebo can help reduce false-positive challenges, it is important to note that false-negative challenges can also occur because of factors such as a subtherapeutic dose, inadequate duration of drug, or a missing cofactor, such as a concomitant infection.

If a patient reports subjective symptoms during a graded challenge, a thorough physical examination should be performed in addition to repeating vital signs. If there are no objective signs of a reaction, the patient should be reassured and informed that such symptoms may or may not be related to the medication administered. The patient should then be provided with the following options: extended observation to assess whether symptoms self-resolve; continuation of the challenge; or discontinuation of the challenge with or without treatment for subjective symptoms (eg, antihistamines for pruritus) with the option of returning for a challenge in the future. Clinicians can also consider readministration of a placebo dose to assess for false-positive reactions. In the study by Iammatteo et al, subjective symptoms that resolved without intervention were deemed not to be allergic and patients were cleared to take the medication without restrictions in the future.

In summary, drug challenges, both single-dose and multiple graded doses, can be a useful tool in the evaluation of patients with MDIS both for delabeling patients with low-risk historical ADRs and for introducing new medications in high-risk patients. The number of steps used in graded drug challenges to evaluate MDIS varies among studies. In a study by Iammatteo et al regarding the safety of graded drug challenges for the evaluation of ADRs in patients with a low-risk history, 1- or 2-step challenges were found to be as safe as multistep challenges comprising 3 or 4 steps. Therefore, the total number of steps used during a graded challenge can be determined by the clinician on the basis of severity of the index reaction in addition to institutional protocols. However, graded drug challenges must be used cautiously in patients who could potentially have MDHS, which is immune-mediated and hypothesized to arise from enhanced responsiveness of T cells to drugs. Patients who experienced any signs or symptoms of a severe immune-mediated DHR should not undergo rechallenge to the culprit drug given the high risk of a subsequent severe DHR.

Addition of placebo to graded drug challenges may help distinguish between allergic and nonallergic challenge reactions. Placebos can be made in the office by mixing a semisolid food, such as yogurt or applesauce, with cherry-flavored pharmaceutical sweetener. The challenge medications, in liquid formulation or crushed pills, should be mixed in the same medium. In the
study by Iammatteo et al on the safety of placebo-controlled graded challenges, patients were informed that they would receive a placebo during the challenge but were not made aware at which step the placebo would be administered.

OPTIONS FOR FUTURE TREATMENT OF PATIENTS WITH CONFIRMED MDHS

For patients with confirmed MDHS, the following options are available: (1) Administration of structurally unrelated medications; (2) Careful administration of a similar but nonidentical medication under observation at the lowest dose possible; or (3) Induction of tolerance (desensitization) for confirmed type I DHRs. The goal is to use the lowest dose of any needed medication for the shortest period possible. It is essential to counsel patients that new adverse reactions are possible with all medication exposures, and they may experience another reaction, likely of the same severity as the index reaction. They should also be informed that subsequent reactions may be completely unrelated to the index adverse reaction because the patient’s age and clinical situation may be different. Challenges need to have enough follow-up time to match the time to onset of reaction(s) after the index exposure. A single therapeutic dose is typically adequate to trigger an immunologically mediated reaction. IgE-mediated hypersensitivity can be triggered by 1/100th of a therapeutic dose. See Figure 2.

CONCLUSIONS

MDIS is defined as non—immune-mediated intolerance to 3 or more chemically unrelated medications. Currently, most documentation of drug “allergy” in the EHR does not differentiate between an immunologic and a nonimmunologic mechanism for ADRs. As a result, physicians are faced with the dilemma of patients having multiple drug “allergies” listed, resulting in prescribing yet additional medications of different classes, adding to increased health care and pharmaceutical utilization, polypharmacy, and a risk of a new drug “allergy.”

Utility of graded drug challenges has proven to be useful in evaluating patients with MDIS. Patients with MDIS should be evaluated by allergy specialists to assist in differentiating ADRs from significant immune-mediated versus non—immune-mediated drug intolerances.

Allergists have the opportunity to think broadly as to why a medication ended up on a specific patient’s do not take list. Although current limitations may exist in many EHRs, relabeling the drug “allergy” field of the EHR in the future may be best accomplished by using more specific categories. Examples include personal preferences (eg, requests for only brand name drugs or a drug without an “artificial” dye); expected side effects (eg, diarrhea with an antibiotic); genetic intolerance (eg, G6PD deficiency); metabolic or disease-specific intolerance (eg, anti-cholinergics in myasthenia gravis, or high-dose NSAIDs in renal failure); situational intolerance (eg, drug-drug interaction, drug X should not be used because drug Y is already being used); structural intolerance (eg, high-dose NSAIDs after bariatric surgery); age-related intolerance (eg, strongly sedating medications in the elderly); and immunologic hypersensitivity (eg, IgE-mediated allergy, direct mast cell activation, or T-cell—mediated hypersensitivity). Delabeling patients from drug “allergy” allows preferred drug treatment regimens as well as introduction of new drugs in a high-risk patient population.

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