Evaluation and management of a patient with multiple drug allergies

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ABSTRACT

Multiple drug allergy syndrome (MDAS) is a clinical diagnosis made in patients with adverse reactions to two or more structurally unrelated drugs with an underlying immune-mediated mechanism causing the reaction. The evaluation of a patient with MDAS begins with a comprehensive drug allergy history and consideration of the underlying immune mechanism for each reaction. Skin testing is a useful diagnostic tool; however, the only validated immediate hypersensitivity skin testing is for penicillin where the antigenic determinants have been identified. Skin testing to most other drugs, although not validated, can be considered using a nonirritating concentration (NIC). In general, skin test positivity using an NIC suggests that the drug should be avoided, but a negative result does not rule out an IgE-mediated allergy. A test dose, also called a drug provocation test, graded oral challenge, or incremental challenge, should be performed when there is a low likelihood of an IgE-mediated mechanism for the reaction. In patients with a recent IgE-mediated hypersensitivity reaction or positive skin testing with no reasonable alternative treatment options, desensitization protocols can be used to allow the patient to safely receive a necessary drug. The evaluation of patients with MDAS is both challenging and time-consuming for the practicing allergist, who must systematically evaluate each reaction to help determine which drugs can be safely used again in the future. The molecular mechanisms and risk factors for this condition remain poorly understood, but research to further understand this condition is ongoing.

(Allergy Asthma Proc 35:197–203, 2014; doi: 10.2500/aap.2014.35.3739)

Allergists are commonly asked to evaluate patients with a reported history of multiple drug allergies. Unfortunately, the terminology for describing adverse drug reactions is poor and confusing, although the differential diagnosis is broad, including hypersensitivity reactions (HSR), drug intolerance, drug idiosyncrasy, pseudoallergic reactions, side effects, or a combination of these different entities (Table 1). When assessing a patient with a history of multiple drug allergies, an allergist must systematically evaluate each reaction to help determine which drugs can be safely used again in the future.

Patients who describe a history of adverse reactions to two or more structurally unrelated drugs that appear to have an underlying immune-mediated mechanism are said to have multiple drug allergy syndrome (MDAS).[1,2] In contrast, multiple drug intolerance refers to a history of multiple nonimmune-mediated adverse reactions to structurally unrelated drugs.[3] Although MDAS appears to be uncommon, the actual incidence and prevalence are unknown.[4–6] Interestingly, published data indicate that patients who describe any drug allergy are likely to report allergies to multiple drugs. In a recent study of drug allergies in patients within one hospital system, 8.7% (7994 patients) reported three drug allergies, 3.8% (3467 patients) reported four drug allergies, 1.7% (1552 patients) reported five drug allergies, and 2.1% reported six or more drug allergies.[7] Similarly, in a cohort of 1893 hospitalized patients needing antibiotics, the majority (85%) reported two or more drug allergies.[8] Although many of these reported reactions are likely not immune mediated, patients and their physicians may be unnecessarily avoiding all of these drugs.

MDAS is a clinical diagnosis, and the pathophysiology and molecular mechanisms of this condition remain poorly understood. Asero *et al.* suggested that MDAS is a distinct entity characterized by an immune response to haptens.[9] Others believe that MDAS may represent a broad range of different immunopathological responses to different drugs.[4] This later view is supported by the observation that about one-third of patients with MDAS have detectable serum levels of histamine-releasing factors.[6] Additionally, patients with MDAS are more likely to react during elective drug challenges with unrelated drugs than those without MDAS.[5] The risk factors for MDAS are unclear; however, research is ongoing to improve our understanding.

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Presented at the Eastern Allergy Conference, West Palm Beach, Florida, June 1, 2013
The authors have no conflicts of interest to declare pertaining to this article
Supplemental data available at www.IngentaConnect.com

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Table 1 **Questions to consider when evaluating a patient with MDAS**

Clinical History	Considerations
Route of administration?	Cutaneous reactions occur with greater frequency in parenterally administered vs orally administered medications
Condition for which drug was prescribed?	Concomitant viral or bacterial infections may trigger urticaria or change reaction threshold (*e.g.* Epstein-Barr virus, human immunodeficiency virus, and mycoplasma)
Alternative drugs available?	If few or no alternative drugs exist, then a more aggressive evaluation may be needed
No. of prior exposures to culprit drug or similar drugs?	IgE-mediated reactions are more likely to occur at least one prior exposure
Other drugs being administered concurrently (particularly nonsteroidal anti-inflammatory drugs, opiates, angiotensin-converting enzyme inhibitors, and/or β-blockers)?	Coadministered drugs may have caused reaction or change the severity or course of the reaction
No. of doses of drug taken before the reaction?	One or two doses may be more suggestive of an IgE-mechanism vs multiple doses or days suggesting a delayed, T-cell–mediated mechanism
Time between last dose of drug and onset of symptoms?	IgE-mediated reactions are most likely to occur within 2–4 hr
Signs and symptoms of the reaction?	It is helpful to document both subjective symptoms and objective evidence of the reaction (oxygen desaturations, tachycardia, hypotension, wheezing, angioedema, urticaria, morbilliform skin eruptions, skin desquamation, and mucosal lesions)
Did symptoms resolve after discontinuation of the culprit drug?	If symptoms persist despite stopping the offending drug, this might suggest alternative etiologies for the reaction
Details of any similar drugs that have been tolerated since the reaction?	If the patient has tolerated a structurally similar medication, this may suggest that the patient is not allergic any longer
Details of any similar symptoms that have occurred despite stopping the culprit drug?	If yes, consider alternative diagnoses such as chronic idiopathic urticaria, dermatographism, systemic mastocytosis, and/or idiopathic anaphylaxis
Duration since the reaction occurred?	If the reaction was remote, the patient may have lost their sensitization (*e.g.* among patients with positive penicillin skin tests, 70–80% will lose this sensitivity after 10 yr)[41]

MDAS = multiple drug allergy syndrome.

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The clinical management of MDAS is both challenging and time-consuming for the practicing allergist. In this article we discuss practical issues to consider when evaluating a patient with MDAS. Our primary goal is to provide the practicing allergist with a standardized approach to the evaluation and management of this complicated clinical issue.

CLINICAL HISTORY AND EVALUATION

Drug Allergy History

The clinical evaluation of any patient with a history of MDAS begins with a comprehensive drug allergy history including the name and dose of the drug, timing and symptoms associated with the reaction, and treatment given for the reaction. If possible, original medical records from the time of the reaction should be obtained for review because clinical history and physical examinations documented by a physician at the time of the reaction are more accurate than a patient's recollection of the event.[10] A suggested list of questions to consider when obtaining a clinical history from a patient with MDAS is detailed in Table 1.[1,2,11]

Classification of HSRs

After taking a thorough history, the underlying mechanisms of the reaction should be considered, including determining if the reaction is likely to be immune mediated (Table 2). For immune-mediated reac-

Table 2 **Classification of adverse drug reactions**

Mechanism of Reaction	Example
Predictable—Type A reactions	
Overdose	Hepatic necrosis from acetaminophen
Side effect	Tremor from albuterol
Secondary effects	Clostridium difficile colitis from clindamycin
Drug–drug interactions	Macrolide antibiotic causing supratherapeutic INR in a patient on Coumadin
Unpredictable—Type B reactions	
Drug intolerance	Tinnitus with aspirin
Drug idiosyncrasy	Hemolysis in patient with G6PD deficiency taking antimalarials
Pseudoallergic reactions	Vancomycin causing red man syndrome
Immune-mediated reactions	
Type I HSR: IgE mediated	Anaphylaxis and urticaria
Type II HSR: IgM or IgG mediated	Hemolytic anemia and organ-specific reactions
Type III HSR: Immune complex mediated	Serum sickness and drug fever
Type IV HSR: Cell mediated	Delayed morbilliform rashes, SJS/TEN, and DRESS/DIHS

Source: Ref. 2.
INR = international normalized ratio; HSR = hypersensitivity reaction; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis; DRESS/DIHS = drug rash with eosinophilic and systemic symptoms/drug-induced hypersensitivity syndrome.

tions, the Gell and Coombs classification system is most commonly used, dividing reactions into types I–IV.[12] Type I HSRs are associated with symptoms of pruritus, rhinorrhea, cough, bronchospasm, angioedema, urticaria, or anaphylaxis. Although most of these HSRs are commonly mediated through IgE, symptoms of type I HSR can result from IgE-independent mechanisms, such as direct mast cell activation.[13] Type II HSRs are mediated through IgG binding to antigen on a cell surface or matrix with subsequent immune system activation. Examples include drug-induced hemolytic anemia and organ-specific reactions, such as a drug-induced nephritis or hepatitis. Type III HSRs are also mediated through IgG but through the formation of soluble antibody–antigen immune complexes. Examples include serum sickness and drug fever. Type IV HSRs are mediated through antigen-specific T cells and often present with delayed rash that appears as a pruritic maculopapular eruption. Although the exact mechanism for many adverse drug reactions are not fully understood, allergic interstitial nephritis, drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome (DRESS/DIHS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN) are likely types II–IV HSRs because these processes are immune mediated but not IgE mediated.

Role of Skin Testing in MDAS

Skin testing should be considered as a diagnostic tool in all patients with immune-mediated drug HSR when an IgE-mediated mechanism is suspected. Skin testing can also be helpful in patients with a history of an ill-defined rash that did not involve mucosal surfaces or result in skin desquamation as well as when the history of the HSR is unknown.[14] Because patients with serum sickness–like reactions can have IgE antibodies and urticaria, in addition to IgM and IgG antibodies, they may have positive skin tests.[15] However, skin testing in serum sickness–like reactions is not recommended.[14] Additionally, skin testing is not appropriate for severe cutaneous reactions (*e.g.*, SJS/TEN, DRESS/DIHS, and exfoliative dermatitis), organ-specific reactions (*e.g.*, hepatitis, interstitial nephritis, and pneumonitis), or autoimmune diseases (*e.g.*, drug-induced bullous pemphigoid, linear IgA bullous disease, drug fever, eosinophilia, or erythema multiforme).

The only validated immediate hypersensitivity skin testing is for penicillin (PCN), where the antigenic determinants have been identified. Skin testing for PCN includes testing to the native drug itself along with the major and minor determinants that have a negative predictive value (NPV) close to 100% and positive predictive value (PPV) of 40–100% (Fig. 1).[14] The major determinant, or benzylpenicilloyl, is commercially available as PrePen (AllerQuest, LLC, Plainville, CT). However, the major limitation of PCN skin testing is that the PCN minor determinants, including penilloate and penicilloate, are not commercially available. Despite this limitation, skin testing with PrePen and PCN G is a useful diagnostic tool and has a NPV of at least 95%.[16,17] Performing PCN skin testing with-

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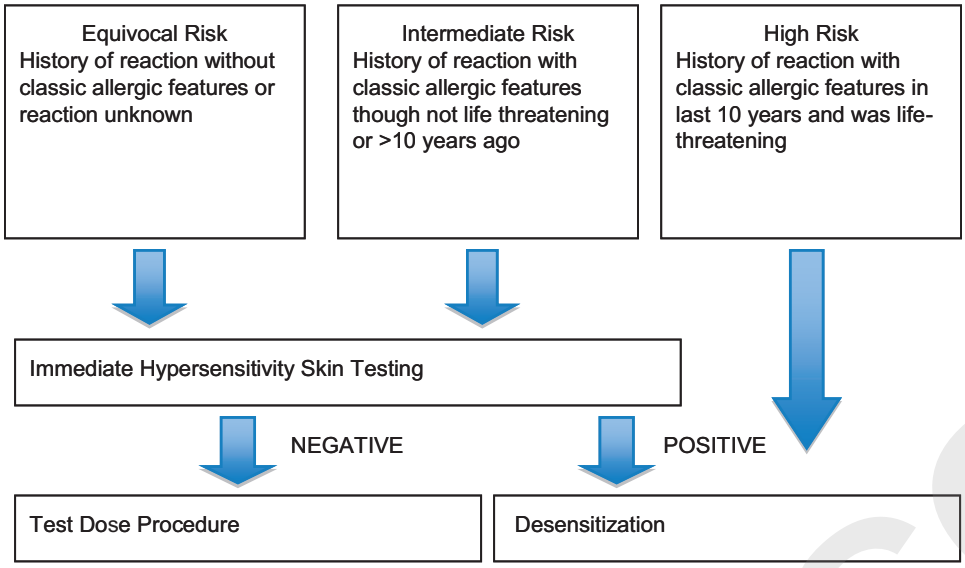


Figure 1. Evaluation of penicillin (PCN) allergy. (Source: Ref. 13.)

Table 3 **NICs of antibiotics for intradermal skin testing**

Class	Drug	Full Strength Concentration (mg/mL)	NIC (as dilution of full-strength concentration)
PCNs	Ticarcillin	200	10^{-1}
	Nafcillin	250	10^{-4}
Cephalosporins	Cefotaxime	100	10^{-1}
	Cefuroxime	100	10^{-1}
	Cefazolin	330	10^{-1}
	Ceftazidime	10	10^{-1}
	Ceftriaxone	100	10^{-1}
Fluoroquinolones	Ciprofloxacin	1	10^{-2}
	Levofloxacin	25	10^{-3}
	Moxifloxacin	4	10^{-3}
Sulfonamides	Cotrimoxazole (Bactrim)	80	10^{-2}
Aminoglycosides	Tobramycin	40	10^{-1}
	Gentamycin	40	10^{-1}
Macrolide antibiotics	Erythromycin	40	10^{-3}
	Azithromycin	100	10^{-4}
	Clarithromycin	50	1 mg/mL
	Clindamycin	150	10^{-1}
Other	Vancomycin	50	10^{-4}

Source: Refs. 14, 40, and 49.
NICs = nonirritating concentrations; PCNs = penicillins.

out minor determinants is helpful in patients with a history of a reaction with classic allergic features that was >10 years ago and not life-threatening, a reaction without classic allergic features, or if the reaction is unknown (Fig. 1). If the reaction occurred in the last 10 years and was life-threatening with classic allergic features, the patient should be considered allergic and skin testing without PCN minor determinants may not be helpful. Additionally, if performing PCN skin testing without minor determinants, it is prudent to follow a negative skin test to PCN and the major determinant with a test dose to amoxicillin.

Skin testing to other drugs, although not validated or standardized, can be considered using published nonirritating concentrations (NICs; Table 3).[14,18] In general, skin test positivity using an NIC suggests that the drug should be avoided, but a negative result does not rule out an IgE-mediated allergy.[19] For example, a recent study tried to validate skin testing for cephalosporin allergy using the NIC and, surprisingly, found that

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Table 4 **Desensitization vs test dose procedure**

	Desensitization	Test Dose
IgE-mediated allergy	Likely	Unlikely
Immune response	Temporarily modifies response	No change in response
Route of administration	By mouth, intravenous, and intramuscular	By mouth, intravenous, and intramuscular
Starting dose	≤1/10,000	>1/100
Number of steps	>5	2
Interval between doses	15–20 min	At least 30–60 min
Monitoring requirements	Continuous monitoring and IV access	No IV, frequent vital signs
Location	Inpatient or outpatient	Outpatient
Maintenance	Requires continued drug administration to maintain tolerance	No need for continued treatment
Future treatment	Requires desensitization	No special precautions

none of the patients who were skin test positive developed an HSR during challenge with a test dose. The four likely IgE-mediated reactions after test dose came from patients who were skin test negative, resulting in an NPV of 99.7% and a PPV of 0%.[20] This supports the need to interpret negative skin tests using NIC with caution. Despite these limitations, skin testing with the NIC can be a clinically useful tool in the evaluation of patients with MDAS.[21]

Macrolide and fluoroquinolone HSRs are frequently reported in patients with MDAS; however, ~90% of these patients are able to tolerate them on rechallenge.[14] Although an NIC to quinolones is published and a negative skin test would be helpful in ruling out an IgE-mediated allergy, validation of skin testing results have been variable with a high false positive rate.[22,23] This has been attributed to the ability of some quinolones to induce histamine release.[24] Similarly, macrolide skin testing with the NIC can be helpful, especially when negative, with a sensitivity of 50–75%, specificity of 72–90%, PPV of 33–36%, and NPV of 82–98%.[25–27]

In addition to antibiotics, skin testing with published NIC may be helpful in evaluating patients with reported reactions to insulin, steroids, local anesthetics, general anesthetics, chemotherapeutic agents, biologics, 5HT3 receptor antagonists, and proton pump inhibitors.[28–36]

Drug Provocation Testing and Desensitization

A test dose, also called a drug provocation test, graded oral challenge or incremental challenge, should be performed when there is a low likelihood of an IgE-mediated HSR. Before recommending a test dose, alternative drugs should be considered. Indications for a test dose include (1) excluding drug allergy in patients whose HSR is not convincing, (2) excluding cross-reactivity in drugs that share a similar structural element (*e.g.*, patients with a PCN allergy who needs a fourth-generation cephalosporin), and (3) excluding allergy for drugs that are not cross-reactive in patients with MDAS because of general apprehension of providers caring for patients with MDAS (Table 4).[5,9,37,38]

Although many variations of this procedure exist in the literature, we suggest a standardized two-step approach.[14] For the first step, give either 1/10 the final treatment dose for an intravenous drug or ¼ of a pill for an oral drug and observe the patient for 60 minutes. If the patient tolerates this step, give the full intended treatment dose of the drug and observe for another 60 minutes. The test dose should be administered in a facility with adequate medical equipment and staff including nursing monitoring, antihistamines, steroids, epinephrine, oxygen, intravenous fluids, and access to a code cart.

If the test dose results in an observable HSR, then it is likely that you have confirmed an immune-mediated allergy. However, the rate of false positive results is high in patients with MDAS.[5,39] This may be because of their increased awareness and anxiety surrounding drug reactions. Interestingly, female gender and >10 reported drug allergies are associated with subjective symptoms, such as pruritus, during a test dose procedure.[25] Therefore, placebo-controlled test doses should be considered for patients with MDAS.[38,40,41]

In patients with a history or evaluation suggestive of an IgE-mediated allergy, the drug should only be given by desensitization or induction of tolerance procedure. This includes patients with a recent history consistent with an IgE-mediated HSR, patients with positive skin testing, and patients who developed an immune-mediated reaction during the test dose. Desensitization protocols are available in the

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literature to most drugs including antibiotics, insulin, chemotherapeutic agents, and biological agents.[14]

Approach to the Management of MDAS

We suggest trying to find at least two classes of antibiotics that are safe for use in each patient with MDAS. We suggest prioritizing the evaluation depending on clinical usefulness of a drug or class of drugs. For example, in a patient with recurrent sinopulmonary infections and MDAS, the main priorities are macrolide and quinolone antibiotics. Cephalosporins and trimethoprim-sulfamethoxazole are the main priorities for a patient with recurrent urinary tract infections. Occasionally, we are referred patients with MDAS who require a specific therapy, such as triple therapy for *Helicobacter pylori* or treatment of latent tuberculosis. In these cases, our evaluation is targeted toward understanding which drugs can be used to optimally treat the patient. To accomplish this, we work with the patient's primary care provider and other specialty providers involved with their treatment.

For patients with MDAS with a history of PCN or early generation cephalosporin allergy, we suggest beginning the drug allergy evaluation with PCN skin testing (PrePen and PCN G). Depending on which antibiotic caused the original allergy, additional skin testing to amoxicillin or a cephalosporin may be performed to evaluate allergy to specific R groups.[42] If the evaluation reveals a negative skin test to PCN, the patient should undergo a test dose to the culprit PCN or cephalosporin before fully clearing the allergy for future use.

Beyond antibiotics, we consider evaluation based on the need for a specific drug. Ultimately, for each reported drug allergy or intolerance, we specify a treatment plan for use in the future by the patient's providers. The recommendation may be based on clinical history, skin testing, and/or test dose results. However, the recommendations for drugs with history of drug fever, SJS/TEN, allergic interstitial nephritis, DRESS/DIHS, eosinophilia, hemolytic anemia, and others will be based on the drug history alone. The recommendation by drug class is either:

- OKAY to use.
- OKAY to use, but initiate treatment with a test dose.
- AVOID because of drug intolerance, idiosyncrasy, or side effect
- AVOID because of immune-mediated reaction
- AVOID because of IgE-mediated allergy, but can be used by desensitization under Allergy/Immunology supervision

We recommend that, whenever possible, drug allergy information be placed directly in the patient's electronic chart by the consulting allergist. Additionally, we recommend sending a letter to the primary care physician and giving a similar copy to the patient (online supplement Fig. E1). For patients with multiple antibiotic reactions, we suggest including a complete list of antibiotics that can be used safely because physician knowledge of cross-reactivity can be variable.[43]

Future Considerations

Currently, our diagnostic testing is only relevant for detection of an IgE-mediated process, but IgE-mediated hypersensitivity represents a small proportion of all immune-mediated drug reactions. Furthermore, our ability to detect IgE-mediated HSR is only fully validated for PCN allergy, and even in the case of PCN allergy, minor determinants are not commercially available for skin testing. For more comprehensive detection of IgE-mediated HSR, we must encourage research to identify the antigenic determinants of the most common drugs causing HSRs.

Although patch testing is not commonly used, it should be considered in the evaluation of morbilliform rashes, acute generalized exanthematous pustulosis and fixed drug eruptions.[44] In addition to skin testing, other methods such as lymphocyte transformation or basophil activation may prove helpful in the evaluation of drug-allergic patients, but more research is still needed.[45,46] Finally, although the sensitivity and specificity of ImmunoCAP for PCN allergy (Phadia AB, Uppsala, Sweden) is not high, hopefully with ongoing research, better diagnostic tools will be available in the near future.[47,48]

As we work to understand the pathophysiology of MDAS, we will improve our ability to provide these patients with the medications they require and their primary care providers with the support they need.

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