Drug Allergy Diagnosis

Anca M. Chiriac, MD[a], Pascal Demoly, MD, PhD[a,b,*]

KEYWORDS

• Drug hypersensitivity reaction • Natural history • Severity signs
• Drug allergy work-up • Imputability

KEY POINTS

- There is no substitute for a proper assessment of the clinical history when a drug hypersensitivity reaction is suspected.
- When assessing a patient with a presumed drug hypersensitivity reaction in the symptomatic phase, it is mandatory to look for severity signs, because they portend a poor prognosis.
- Confirmation of a drug hypersensitivity relies mostly on in vivo tests, and their contraindications must be rigorously observed.
- The available literature does not answer the numerous questions regarding the natural history of drug hypersensitivity. When the diagnosis is confirmed, lifelong avoidance of the drug causing the reaction is recommended.

INTRODUCTION

Drug allergy that is poorly documented and often self-reported is a frequent problem in daily clinical practice and has a considerable impact on prescription choices. When drug reactions resembling allergy occur, they are called drug hypersensitivity (DH) reactions (DHRs) before showing evidence of either drug-specific antibodies or T cells. The term drug allergies should be reserved for immunologically mediated DHRs. The diagnostic work-up of DHRs allows a better classification of the reactions and provides patients with more reliable information and recommendations for future treatments. Several guidelines and consensus documents on general or specific drug class–induced DHRs are available to support the diagnosis. This article is based on the recent International Consensus (iCON) on Drug Allergy,[1] a consensus that was reached by leading allergy organizations worldwide (the European Academy of Allergy

Disclosure Statement: The authors declare no conflict of interest for this work.
[a] Allergy Unit, Respiratoty and Addictology Department, Hôpital Arnaud de Villeneuve, 371, Avenue du Doyen Gaston Giraud, University Hospital of Montpellier Cedex 5, Montpellier 34295, France; [b] Sorbonne Universités, UPMC Paris 06, UMR-S 1136, IPLESP, Equipe EPAR, Paris 75013, France
* Corresponding author. Allergy Unit, Département de Pneumologie et Addictologie, Hôpital Arnaud de Villeneuve, 371, Avenue du Doyen Gaston Giraud, University Hospital of Montpellier Cedex 5, Montpellier 34295, France.
E-mail address: pascal.demoly@inserm.fr

Immunol Allergy Clin N Am 34 (2014) 461–471
http://dx.doi.org/10.1016/j.iac.2014.03.002 **immunology.theclinics.com**
0889-8561/14/$ – see front matter

and Clinical Immunology [EAACI], the American Academy of Allergy Asthma and Immunology [AAAAI], the American College of Allergy Asthma and Immunology [ACAAI] and the World Allergy Organization [WAO]) to synthesize multiple guidelines into 1 generally approved and accepted consensus document.

CLINICAL MANIFESTATIONS

DHRs are classified artificially into 2 types, according to the delay of onset of the reaction after the last administration of the drug: (1) immediate reaction, occurring less than 1 hour after the last drug intake, usually in the form of isolated urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm, gastrointestinal symptoms (nausea, vomiting, diarrhea), or anaphylaxis with or without cardiovascular collapse (anaphylactic shock); and (2) nonimmediate reaction, with variable cutaneous symptoms occurring after more than 1 hour and up to several days after the last drug intake, such as late-occurring urticaria, maculopapular eruptions, fixed drug eruptions, vasculitis, blistering diseases (such as toxic epidermal necrolysis [TEN], Stevens-Johnson syndrome [SJS], and generalized bullous fixed drug eruptions), drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), and symmetric drug-related intertriginous and flexural exanthemas. Internal organs can be affected either alone or with cutaneous symptoms including hepatitis, renal failure, pneumonitis, anemia, neutropenia, and thrombocytopenia. The first category is mostly mediated through specific immunoglobulin E (IgE), whereas the second is specific T cell mediated. For specific descriptions, the readers are referred to previous issues of *The Clinics of North America*.[2,3]

SEVERITY SIGNS OF DHRS

When assessing a patient with a presumed DHR in the symptomatic phase, it is mandatory to look for severity signs and, after doing so, to update the risk/benefit balance of exploring the suspected drug(s) on a case-by-case basis.

Severity (danger) signs may include both clinical symptoms and biological/laboratory parameters, according to the type of reaction.[1] Some are well-established criteria and have been assigned individual weights in scoring systems for classifying the severity of delayed reactions.[4]

Severity signs are either obvious to the naked eye (clinical), or invisible (mainly biological) (**Table 1**). The latter must be looked for thoroughly, to reveal internal organ damage.

In immediate reactions, the clinical picture is self-explanatory. Symptoms develop rapidly and cutaneous and mucosal involvement may quickly escalate toward life-threatening airway, breathing, or circulatory problems. Measurements of histamine or tryptase have no value for the therapeutic management in the acute setting, but may a posteriori support the diagnosis of allergic anaphylaxis, especially in cases of drug allergy in perioperative settings.[5]

Nonimmediate reactions are more heterogeneous and there may be overlap between different patterns. When confronted with a suspicion of a delayed DHR, both general and organ-specific severity/danger signs must be systematically looked for (see **Table 1**). Daily reevaluation is mandatory to identify progression or signs of recovery.

Regardless of the type of reaction, the presence of severity signs warrants the immediate withdrawal of the suspected drug(s), appropriate supportive treatment of the patient, and special care later during the exploration phase. However, in the absence of these signs and if the drug is mandatory, treating through might be an option.