Drug hypersensitivity reactions: an overview

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Keywords

Drug hypersensitivity; hypersensitivity; immunoglobulin E; T-lymphocytes; penicillins; diagnostic errors.

Abstract

Drug hypersensitivity reactions (DHRs) account for 10% of all adverse drug reactions.

DHRs are clinically classified as immediate, mostly drug-specific IgE antibody (sIgE) -mediated, and nonimmediate, mostly T-cell mediated, reactions. Gathering insights into the underlying pathophysiological mechanism is crucial for correct orientation of further diagnostic work-up of DHRs. Therefore, a thorough history focusing on elements such as signs, symptoms, timing, index drug, re-exposition is of paramount importance. In case of immediate DHR, diagnosis may comprise skin testing with immediate readings, sIgE antibody quantification, specialized *in vitro* diagnostics. In nonimmediate DHR, sIgE antibodies are not useful and skin tests are performed with delayed readings. In difficult cases with negative or uncertain test results, eventually a drug challenge might be required to document or refute diagnosis.

Correct diagnosis of DHRs is very important. Unverified and false diagnoses of "drug allergy", mainly "penicillin allergy", have evolved into a plague with increasing medical and financial burden. On the other hand, misdiagnosis entails a risk for potentially life-threatening and fatal reactions upon re-exposure. Therefore, quick referral for an allergy workup in case of a possible DHR is recommended.

Introduction

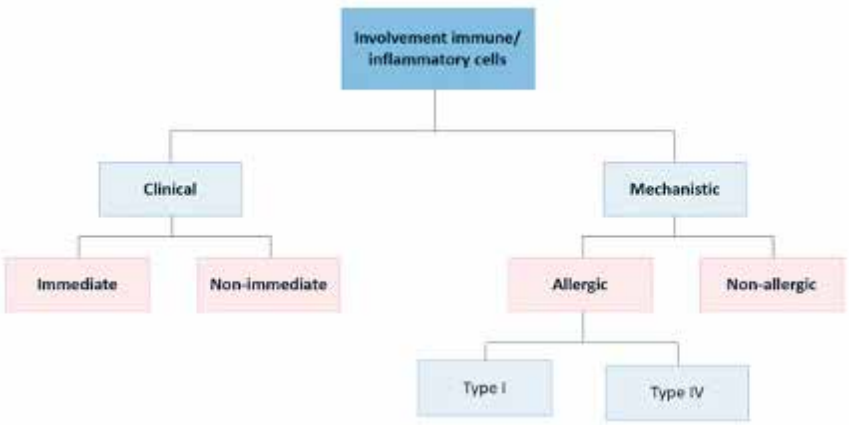
Adverse drug reactions (ADRs) are defined as unintended, harmful effects resulting from exposure to a compound for diagnostic, prophylactic, or therapeutic purposes. Most ADRs directly dependent on the pharmacological properties of the drug (e.g. bleeding by anti-coagulants). Drug hypersensitivity reactions (DHRs) on the other hand, comprise symptoms resulting from effects extending beyond the pharmacological targets of a drug and can result from the activation of immune cells, inflammatory pathways, or both. DHRs account for 10% of all ADRs. According to the World Allergy Organization (WAO), DHRs occur in 1% to 2% of all admissions and in 3% to 5% of the hospitalized patients. The true prevalence in the community is unknown. However, despite absence of correct prevalence data in children, DHR are estimated to be less frequent than in adults, possibly because of less exposure to drugs.

As shown in *Figure 1*, DHRs can be classified based upon their clinical presentation (chronology and morphology) and/or based upon their underlying pathophysiological mechanism.

According to the underlying pathophysiologic mechanism, DHRs can be further subclassified as allergic or non-allergic. Allergic hypersensitivity involves specific activation of drug-reactive T- and/or B-cells of the adaptive immune system (1). T-cells are involved in both immediate and nonimmediate allergic reactions. In contrast, B-cells are only involved in IgE-mediated immediate allergic reactions. Traditionally, 4 types of allergic DHRs are described according to the Gell and Coombs classification (table 1) (2). Type I (mostly mediated by drug-specific IgE antibodies (sIgE)) and type IV (cell mediated) reactions are the most frequent encountered reactions.

In contrast, non-allergic immediate DHRs (IDHRs) involve activation of

Figure 1: Classification of drug hypersensitivity reactions.



immune cells and release of mediators by direct mechanisms independent from the adaptive immune system response (e.g., mast cell activation via activation of the mas-related G protein-coupled receptor type X2 (MRGPRX2) or due to pro-inflammatory mediators increased by COX-1 inhibition). Established MRGPRX2-agonists are opiates, quinolones, and neuromuscular blocking agents (3, 4, 5). However, these drugs can also trigger sIgE-dependent basophil and mast cell degranulation. Non-allergic nonimmediate DHRs (NIDHRs) can also result from pharmacological interaction between a drug and MHC of the antigen-presenting cell or T-cell receptor (6).

As shown in figure 1, from a clinical point of view, DHRs are clinically classified as immediate and nonimmediate reactions, designated respectively as IDHRs and NIDHRs. Immediate reactions usually occur within 1 hour, also depending on the route of exposure, and the clinical presentation varies from single organ involvement (e.g., urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm) to potentially life-threatening anaphylaxis (*see figure 2*). Mechanistically, most IDHRs rest upon the activation of tissue-resident mast cells and/or circulating basophils. In contrast, NIDHRs occur more than 1 hour after the exposure (often 48-72h later) and mainly manifest as a maculopapular exanthema or, much rarer, as serious cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome. These NIDHRs involve the activation of drug-specific T-cells, but not mast cells nor basophils. However, correct allocation of the individual patient to one of these phenotypes can be extremely difficult, if at all possible. Therefore, rapid referral of a patient with a possible drug allergy including a detailed description of the clinical presentation is crucial.

Gathering insights into the underlying pathophysiological mechanism is crucial for correct orientation of further diagnostic work-up of DHRs. A thorough history (and revision of medical records) is of paramount importance. Information about signs (photos when available), symptoms, time of onset of the DHR, treatment of the DHR, index drug, indication for the β-lactam antibiotic, other medication concurrently used, persistence of the signs and symptoms after stopping the medication, re-appearance of the signs and symptoms in absence of the index drug and re-administration of the same drug after the reaction, must be obtained. This information is necessary to differentiate between an IDHR or a NIDHR. Moreover, history (e.g., on the timing of the reaction in response to the last dose of the drug) can be helpful for individual risk stratification. A recent study of our research group showed that an urticarial eruption that appearing within 1 hour after the first intake and regressing within 1 day was significantly more frequently observed in patients with a positive skin test/serum specific IgE assay (1-1-1 criterion) (7).

Figure 2: Sings/symptoms of immediate drug hypersensitivity reactions.

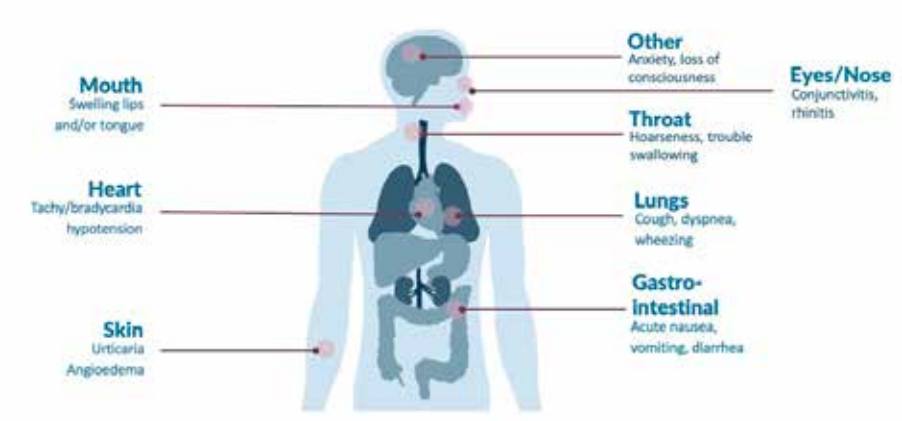
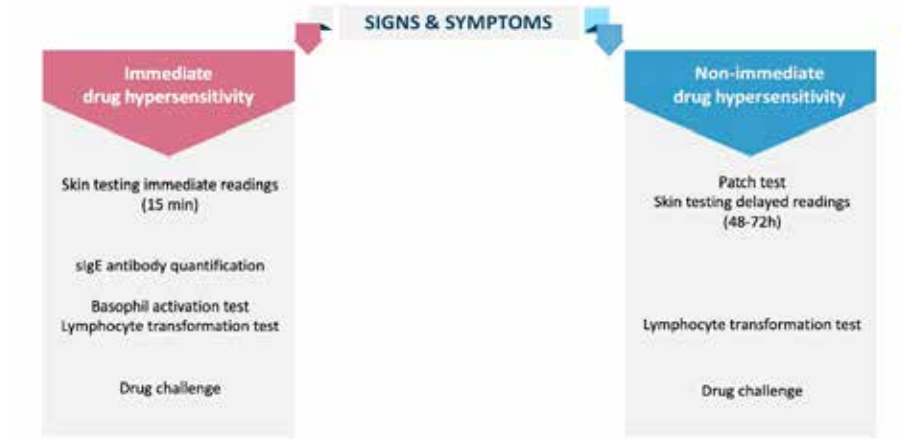


Figure 3: Algorithm for the diagnosis of immediate drug hypersensitivity reactions (IDHRs) and nonimmediate drug hypersensitivity reactions (NIDHRs) (adapted from (17)).



However, the discrimination between IDHR and NIDHR is not always straightforward. Sadly, very often, patients do not remember the exact timing and clinical features of their "index reaction", as it often occurred decades ago during childhood or adolescence. In these cases, finding out the clinical phenotype is often extremely difficult, if possible at all. In such patients, international guidelines recommend combining diagnostics for immediate and nonimmediate reactions (8). It goes without saying that such a combined approach increases risk and cost. Therefore, quick referral for an allergy workup in case of a possible DHR is recommended.

Confirmatory diagnostics

As mentioned before, further diagnostic work-up is guided by history and the suspected underlying pathophysiological mechanism. Figure 3 shows the diagnostic algorithm of IDHRs and NIDHRs according to the current recommendations (9, 10).

IDHR

Paired serum tryptase

The pathophysiology of IDHRs relies upon the activation and degranulation of mast cells and basophils. Tryptase is a trypsin-like protease that is mainly stored in intracellular mast cell granules. Alfa- and β- protryptase monomers are released spontaneously by resting mast cells. Other α- and β- protryptase monomers are converted

to mature tryptase which is released upon mast cell degranulation. Consequently, an increase in serum tryptase is supportive for mast cell activation.

Thus, paired quantification of acute and basal tryptase is recommended in patients with a suspected IDHR. Acute tryptase should ideally be measured 30 to 120 minutes after the onset of the reaction. Basal tryptase levels should be obtained before the event or at least 24 hours after resolution of all signs and symptoms. The current consensus formula for mast cell activation is a serum acute tryptase level equalling or exceeding 1.2x baseline serum tryptase +2 (11). So even if the value of tryptase at the time of the reaction seems to be normal, that is below 11.4 µg/L, a basal tryptase must be obtained in order to exclude mast cell activation. Noticeably, the absence of mast cell activation does not exclude an IDHR.

Further diagnosis of IDHRs is limited to the demonstration of an IgE-dependent reaction, as no diagnostic is available to demonstrate alternative processes such as mast cell activation via off-target occupation of MRGPRX2 (5). IgE-dependent reactions can be documented *in vitro* by quantification of specific drug-reactive IgE (sIgE) antibodies and in vivo skin prick tests and/or intradermal tests with immediate readings.

Skin testing

Today, skin prick testing (SPT) and intradermal testing (IDT), constitute the primary confirmatory step in the diagnostic work-up of an IDHR. Skin prick tests are performed on the ventral part of the forearm and imply a saline buffer solution (negative control) to exclude cutaneous hyperactivity, histamine 10 mg/mL (positive control) to assess skin test reactivity and the involved drugs. SPT are read after 15 minutes and considered positive when the wheal equals or exceeds 3 mm with a surrounding flare. IDT are read after 20 minutes and, for most drugs considered positive when the wheal, accompanied by an erythema, equals or exceeds 5 mm or is doubled as compared to the injection bleb.

Even though skin tests are the first step in the diagnostic work-up of a potential DHR, there are still some disadvantages to be mentioned.

First, skin tests are sometimes unreliable, such as in patients with cutaneous anergy or patients taking antihistamines both leading to false negative readings. False positive results, on the other hand, can be seen in patients with dermographism. Second, skin testing is not always recommended (e.g., for fluoroquinolones and opiates, skin tests have no added value due to low specificity) (12). Third, skin test performance is highly dependent on the methodology and operator used. Furthermore, for many drugs, the maximal non-irritant concentration (NIC) for skin tests have not been established and have mainly been established in healthy control individuals or have been generalised for all compounds in a certain drug class without correct validation. Besides, NICs might vary for IDHRs and NIDHRs (13). Further validation of NICs is crucial for optimization of sensitivity and specificity of skin tests.

Quantification of total and drug specific IgE antibodies

Quantification of total and drug specific IgE (sIgE) antibodies can be used in the diagnosis of IDHRs. However only a limited number of drug-specific assays are available and sensitivity and specificity of sIgE assays for drugs vary significantly (14). Recently, it has been suggested that, to optimize sensitivity, the threshold for positivity of sIgE has to be lowered to 0.10 kUA/L instead of 0.35 kUA/L. However, a recent study of our research group (15), showed that all patients with a suspected immediate, non-life-threatening, hypersensitivity to amoxicillin or a non-specified penicillin and a sIgE to penicillins between 0.10 kUA/L and 0.35 kUA/L, underwent a drug challenge without any problems. Diagnosis of penicillin hypersensitivity should not rest upon a low sIgE result alone.

Drug challenges

Drug challenges (DCs) are the reference test to correctly diagnose IDHRs (16). However, DCs entail a risk for (severe) complications and even DCs are not absolutely predictive for the clinical outcome of subsequent exposure with a risk for false negative results (17). Therefore, DCs should be preceded by skin and/or sIgE testing. However, sometimes, in low-risk patients a direct drug challenge can be considered. Traditionally, DCs imply the administration of incremental doses of the suspected drug(s) with a minimum interval of 30 minutes under strict hospital surveillance with emergency room facilities. A minimum observation period of 2 hours after the last dose is recommended. A challenge test is only considered positive when objective symptoms (e.g. hypotension, urticaria, angioedema, wheezing,…) can be observed.

Basophil activation test (BAT), mast cell activation test (MAT) and lymphocyte transformation test (LTT)

As DCs are hampered by the risk of severe, life-threatening reactions and are demanding in resources, time consuming and costly (17), flow-based analyses of basophil activation (BAT) as potential complementary diagnostic for immediate drug allergy have been studied. Although the BAT has become a pervasive test for IDHRs, expert consensus has not been reached. For example, for β-lactam antibiotics, the sensitivity of BAT varies between 13 and a too optimistic 67% (18, 19). The reasons for this poor sensitivity mainly relate to a basophil non-responder status as seen in 10-15% of our patients and rapid negativization of BAT over time (20). Negativization also applies to sIgE and skin tests (21, 22). Importantly, the loss of reactivity in skin testing, quantification of sIgE and BAT, is not necessarily accompanied by loss of clinical reactivity. Whether the passively sensitized mast cell activation test (MAT) might overcome these limitations is a matter of ongoing attractive research. However, because of the rapid decline of sIgE titers, it seems unlikely the MAT will close the gap in the diagnosis if IDHRs to β-lactams. T-cell tests, such as the lymphocyte transformation test (LTT) and variants such as flow-based analysis of activation markers and cytokine expression have only been rarely adopted to document IDHRs (23).

NIDHRs (type IV)

Skin testing

Skin testing procedures for NIDHRs include patch testing and delayed readings of the IDT. Patch testing is a simple and safe diagnostic with a low risk of systemic reactions. In a patch test the drug is generally dissolved in petrolatum and this mixture is applied to the skin of the back. Readings are done after 72-96 hours. Patch testing is considered positive when erythema, infiltration and papules can be observed. Patch testing is the method of choice in patients who experienced SCARs (17). In cases of positive patch tests, further IDTs should be avoided, whereas in cases of negative patch test, IDTs can eventually be performed (9, 10) provided there is no contraindication such as drug-induced autoimmune diseases, severe exfoliative skin reactions and severe vasculitis syndromes .

The technique of IDTs is already described higher. However, for NIDHRs delayed readings of IDT after 48-96 hours are necessary. Delayed readings of IDT are considered positive when an induration surrounded by erythema exceeding 5mm occurs (24). In maculopapular exanthema (MPE), IDTs have a higher sensitivity as compared to patch testing. Therefore, in MPE IDTs are performed without prior patch testing (24).

However, like skin tests for immediate drug allergy, non-irritating concentrations have not yet been established and skin tests are not absolutely predictive. Consequently, again, many patients will need additional DCs to confirm or refute diagnosis.

Drug challenge

As in IDHRs, DC is the reference test for diagnosis of NIDHRs after negative skin testing including delayed readings of IDT and/or patch testing (17). DCs are contraindicated in patients with SCARs and patients with hematologic reactions, e.g. vasculitis (17). As exemplified higher, traditional DCs imply administration of incremental doses of the suspected drug(s) in a single-day. However, for NIDHRs signs and symptoms are expected to occur hours to days after the DC. Prolonged DCs, extending over several consecutive days seem to be of limited use in the diagnosis of nonimmediate drug hypersensitivity (25). It is of utmost importance to balance accuracy, safety, cost, and labor intensity of diagnostic procedures in beta-lactam allergy. Currently, there is increasing evidence for direct challenges in mild NIDHRs. A recent systematic review and meta-analysis (26) showed that in these "low risk" children direct challenges without prior skin testing are effective and safe. However as acknowledged by the EAACI Task Force report (9), hitherto, there is no clear and uniform definition of "mild" and "low-risk". Further studies on this subject are needed with specific focus on children as their risk profile differs from adults.

Lymphocyte transformation test and variants

There are many in vitro techniques to identify causative agents for NIDHRs such as the LTT, cytokine/mediator detection assays, multiplex bead-based immunoassay and ELISpot. The LTT is the most standardized method but failed to enter mainstream use. The main limitations of the traditional LTT are the need for radioactive thymidine, long culture duration (4-7 days) and poor sensitivity (27). Other in vitro tests, like cytokine detection assays, have also been used, but they are still being evaluated. In the last few years, the advent of performant multicolor flow cytometers has paved the way for the development of novel and more practicable techniques (28). The main advantages of these flow cytometric assays over traditional LTT are speed (48-72h vs. 6 days) and the fact that they do not require a radioisotope. A study of our research group showed that the intracellular quantification of CD154 is an attractive instrument to document both nonimmediate allergies to amoxicillin (clavulanic acid). Most importantly, the test yielded positive results in patients with negative skin tests who needed additional DCs to document diagnosis and it seems that drug-specific T-cell responses might be longer detectable after the index reaction than other diagnostic techniques (29). However, further research is required.

The scourge of unverified "penicillin allergy"

β-lactam antibiotics (β-LABs), especially penicillins, are one of the predominant causes of drug hypersensitivity reactions (DHRs) with significant morbidity and mortality. Alternatively, unverified and false "penicillin allergies", mainly to the first-line preparations natural penicillin and aminopenicillins, have evolved into a plague with increasing medical and financial burden. A recent study on the prevalence of self-reported penicillin allergy in a Belgian outpatient population showed that 12% of the individuals attending the outpatients' allergy clinic claimed to have a "penicillin allergy". However, over 90% of the cases with such a spurious "penicillin allergy" tolerate a challenge with the alleged culprit(s) (30). Importantly, unverified "penicillin allergy" constitutes an almost life-long condition that generally starts as an ill-described, ambiguous and undocumented history in childhood/adolescence going unchallenged in adulthood.

The negative consequences of spurious allergy are undeniable, not only for the individual patient, but also for society. Actually, spurious "penicillin allergy" is associated with erroneous avoidance and unnecessary substitutions, readmissions, poorer outcomes, prolonged hospitalizations, increased costs and last but not least increased rates of *Clostridium difficile* and antimicrobial resistance. On the other hand, misdiagnosis entails a risk for potentially life-threatening and fatal reactions upon subsequent exposure.

In conclusion, judicious diagnostic work-up by a trained physician is absolutely necessary in every case of both witnessed or self-reported "penicillin allergy. The importance of a correct and complete description of the index reaction, eventually complemented with pictures of skin lesions, cannot be overemphasized. Every referring physician who witnesses a potential drug hypersensitivity reaction should provide a complete and correct report. This information is critical for guidance of further diagnostic testing and will help to avoid unnecessary tests, which is especially important in children. Further efforts to simplify and optimize the diagnostic approach, to control the plague of alleged "penicillin allergy" and to correctly label patients as truly allergic are needed.

Conflict of interest

The authors have no conflict of interest to declare with regard to the subject discussed in this manuscript.

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