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Drug Allergy (MJ Torres Jaén, Section Editor)

Precision Medicine in the Management of Drug Allergy

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Abstract

Purpose of study The term precision medicine has been developed in the last five or more years to describe the concept of treating patients individually based on a variety of factors. Precision medicine can be applied to the field of drug allergy where phenotypes, endotypes, and biomarkers have been defined.
Recent findings Phenotypes of drug allergy can be based on (1) the mechanism of the underlying reaction; (2) the clinical presentation of the reaction; and (3) the timing of the reaction in regards to exposure to the drug. Endotypes of drug allergy can be defined based on mechanisms, pharmacologic processes, and human leukocyte antigen haplotypes. Lastly, biomarkers utilized in drug allergy include skin tests, specific IgE tests, basophil activation tests, cellular-based assays, mediator measurement, drug patch tests, and genotyping. The approach to penicillin allergy in recent years highlights the application of precision medicine in drug allergy.

Introduction

The term precision medicine has been developed in the last five or more years to describe the concept of treating patients individually based on a variety of factors. A similar term "personalized medicine" was defined around the same time, but the term "precision medicine" is preferred since most physicians have always treated patients on a personalized level. Precision medicine is most frequently thought of in regards to cancer therapy where individualized care can be tailored based on the patient's specific genetic profile and medical history. In this field, technologies such as genomics, biobanking, and computational biology have all been utilized. Furthermore, some authors have defined precision medicine more as a process than necessarily an endpoint [1].

Precision medicine is not always in the context of cancer treatments and can be applied to many other disciplines of medicine including Allergy and Immunology. A recent PRACTALL document (a joint effort of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma and Immunology) from 2017

reviewed literature on how precision medicine could be approached for food allergy, anaphylaxis, and drug allergy [2••]. This document discussed literature on defining these allergic disorders based on specific phenotypes, endotypes, and biomarkers. The purpose of this review will be to expand the discussion of precision medicine as it applies to the management of drug allergy along with some specific examples of how this information has been utilized in recent years.

Phenotypes of drug allergy

While many healthcare practitioners view drug allergy as one disease entity, it is quite clear that drug allergy or drug hypersensitivity reactions represent a large spectrum of different immunologic and nonimmunologic reactions. Clinical characteristics of drug hypersensitivity reactions have been long recognized and defined; however, uniform systems for organizing and classifying these reactions are lacking. Like many other allergic disorders, drug hypersensitivity reactions encompass a heterogeneous group of disorders. Classification schemes utilized to organize hypersensitivity reactions are often based on clinical or mechanistic traits. The most common classification systems used are based on (1) the mechanism of the underlying reaction; (2) the clinical presentation of the reaction; and (3) the timing of the reaction in regards to exposure to the drug (Table 1).

Table 1. Phenotypes of drug allergy

Mechanistic phenotypes	Examples
Gell and Coombs	
Type I	Anaphylaxis
Type II	Autoimmune hemolytic anemia
Type III	Serum sickness
Type IV	Maculopapular exanthem
Pseudoallergic	Icatibant-induced local reactions via MRGPRX2
Cytokine release syndrome	Rituximab-induced fever, nausea, hypotension
Pharmacologic effects	Aspirin exacerbated respiratory disease
Unclear	SJS/TEN
Clinical phenotypes	
Cutaneous	Exanthems, urticaria, fixed-drug eruptions
Organ-specific	Drug-induced liver injury
Multiorgan	Serum-sickness like reaction
Chronologic phenotype	
Immediate reaction	Urticaria 20 min after penicillin
Delayed reaction	DRESS

Mechanistic phenotypes

One of the oldest classification schemes for drug hypersensitivity reactions comes from the landmark 1963 book by the British immunologists Philip Gell and Robert Coombs [3]. The oft referred to Gell and Coombs hypersensitivity classification system introduced four principal types of hypersensitivity types I–IV, based on underlying immunologic mechanisms. While this immune-based classification system is still utilized today in the management of drug hypersensitivity, many drug reactions do not neatly fit into this system. Thus, while outdated, the Gell and Coombs classification is not completely obsolete.

Pseudoallergic reactions have long been recognized and referred to as nonspecific mast cell activation reactions. These reactions do not fit into the Gell and Coombs classification system. In 2015, a group led by Dong identified the human G protein-coupled receptor MRGPRX2 as a mast cell-specific receptor critical for pseudoallergic drug reactions to drugs such as ciprofloxacin, icatibant, and neuromuscular blocking agents such as atracurium [4••]. MRGPRX2 has also been suggested in the pathogenesis of chronic urticaria, itch, and asthma [5]. The identification of small molecule inhibitors or monoclonal antibodies to MRGPRX2 may be therapeutically useful in management of pseudoallergic reactions, which can be severe and cause anaphylaxis.

Cytokine release syndrome (a.k.a cytokine storm) is another phenotype of drug hypersensitivity not captured in the Gell and Coombs system. These reactions are caused by release of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 and can result in a myriad of symptoms including fever, chills, hypotension, and multiorgan failure [6]. The most common drugs shown to induce cytokine release syndrome include monoclonal antibodies, but chemotherapeutics have also been noted to cause similar reactions. Chimeric antigen receptor (CAR)-modified T cells used in targeted cancer therapies have also been shown to cause cytokine release syndrome, and the use of the IL-6R antagonist tocilizumab was shown to reverse this cytokine release syndrome [7].

Pharmacologic effects of drugs are key to pharmacotherapy but may also be involved with drug hypersensitivity reactions. The key example of this is with aspirin/NSAID hypersensitivity reactions. While there are multiple phenotypes of aspirin/NSAID reactions, some of these are specifically related to inhibition of COX1 (cyclooxygenase-1) with subsequent activation of mast cells, eosinophils, and other effector cells and release of inflammatory mediators including leukotrienes. Recently, platelet-adherent granulocytes have been shown to be important in the pathogenesis of aspirin-exacerbated respiratory disease (AERD) and serve as a rich source of LTC4 synthase and generation of cysteinyl leukotrienes [8••]. While AERD is the most well-known of these syndromes, NSAID-exacerbated cutaneous disease and NSAID-induced urticaria and angioedema are other examples of pharmacologically mediated drug reactions.

Finally, a number of delayed severe cutaneous adverse drug reactions (SCAR) have unclear mechanisms that may involve classical features of delayed-type hypersensitivity but other mechanisms as well. These severe cutaneous reactions can be caused by T cell activation through processes such as the pharmacologic interaction (p-i) model or the altered repertoire model [9]. In addition, other mechanisms involving cytotoxic CD8+T cells and innate activation leading to apoptosis may also be involved in some of these reactions. Viral reactivation and heterologous immunity (e.g., molecular mimicry

between prior virus and drug exposure) also plays a role particularly in the drug reaction with eosinophilia syndrome (DRESS) [10].

Clinical phenotypes

Drug hypersensitivity reactions can also be phenotyped based on clinical presentation. Classification schemes have been proposed based on single organ-specific drug reactions as well as multiorgan drug reactions [11].

The most common clinical manifestation of drug hypersensitivity reactions is with involvement of the skin. There are a variety of cutaneous manifestations of drug hypersensitivity with common reactions including urticaria, angioedema, fixed drug eruptions, and pustules. More severe cutaneous drug reactions often with multiorgan involvement include DRESS, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP). Numerous less common cutaneous drug reactions may also occur including bullous eruptions, lichenoid eruptions, cutaneous lupus erythematosus, photosensitive reactions, and pupura [12].

Noncutaneous organ-specific drug hypersensitivity reactions are also well described. Hematologic reactions including hemolytic anemia, thrombocytopenia, and granulocytopenia are often immunologic based. Drug-induced liver injury may have a number of mechanisms including toxicity due to drug metabolites, innate immune activation, and adaptive immune activation [13]. Drug-induced liver injury typically presents as hepatitis or cholestatic injury. Drug-induced pulmonary hypersensitivity reactions can present in a number of ways including hypersensitivity pneumonitis, interstitial fibrosis, eosinophilia, and pleural effusions. Drug-induced renal hypersensitivity can present as isolated interstitial nephritis or membranous glomerulonephritis or as part of a more severe drug reaction such as with DRESS.

Lastly, multiorgan reactions can also be a manifestation of drug hypersensitivity with the classic example being anaphylaxis. All of the SCAR can have multiorgan involvement as well as systemic drug-induced lupus erythematosus, and drug-induced vasculitis. Serum sickness and the more common serum sickness-like reactions typically present with cutaneous rashes, fever, and arthralgias.

Chronologic phenotypes

Immediate drug reactions

Immediate drug reactions in the past were defined as occurring within an hour of drug exposure but have now been expanded to within 6 h of exposure to a drug [2, 14•]. While many immediate drug reactions are due to IgE-dependent mechanisms, pseudoallergic reactions and even cytokine release syndrome may occur in this timeframe.

Delayed drug reactions

Nonimmediate (delayed) drug reactions are defined as occurring more than 6 h after drug exposure. Some delayed reactions are accelerated occurring within hours of exposure often due to pre-existing antibodies or memory T cells, while more typical delayed drug reactions develop over days. DRESS is a unique

reaction that typically develops several weeks after an initial drug exposure. Drug-induced systemic lupus can also develop over several months of drug therapy and numerous organ-specific reactions may take months of exposure to become clinically apparent.

Endotypes in drug allergy

Several endotypes exist for drug hypersensitivity reactions. These endotypes can be defined based on mechanisms, pharmacologic processes, and human leukocyte antigen (HLA) haplotypes (Table 2).

IgE-mediated endotype

IgE-mediated endotypes are one of the best described of the drug hypersensitivity endotypes. This endotype requires a period of sensitization to either the culprit drug or a cross-reacting substance which results in production of drug-specific IgE. Phenotypically, these present as immediate reactions and have been described for numerous medications including antibiotics, chemotherapeutics, NSAIDs, monoclonal antibodies, perioperative medications, and even corticosteroids. This endotype is defined most commonly through skin testing, but other forms of in vitro testing may also be used.

Pseudoallergic endotype

Pseudoallergic endotypes do not require sensitization and are independent of an adaptive immune response. Multiple mechanisms may result in pseudoallergic reactions but are related to direct activation of mast cells through various pathways including opioid, complement, and MRGPRX2 receptors. Phenotypically, these present as immediate reactions and may occur with the first drug exposure. Typical examples of drugs capable of pseudoallergic reactions include opiates, vancomycin, quinolones, and some neuromuscular blocking agents. This endotype is diagnosed often historically based on the culprit drug involved. Evidence of elevation in mast cell mediators and the lack of drug-specific IgE can be supportive.

Table 2. Endotypes of drug allergy

	Examples
IgE-mediated endotype	Anaphylaxis to carboplatin due to FcεRI-triggered mast cell activation
Pseudoallergic endotype	Vancomycin red man syndrome due to nonspecific mast cell activation
T cell-mediated endotype	Drug-induced baboon syndrome due to drug-specific T cells
Aspirin-exacerbated respiratory disease	Wheezing and rhinitis after ibuprofen due to COX-1 inhibition and dysregulation of 5-lipoxygenase-LTC4 synthase pathway
HLA-associated drug hypersensitivity endotype	HLA-B*57:01 and abacavir hypersensitivity syndrome due to altered peptide repertoire reaction

Table 3. Biomarkers of drug allergy

	Examples
Immediate skin test	Penicillin skin tests
Specific IgE tests	ImmunoCAP® for chlorhexidine
Basophil activation test	CD203c expression for carboplatin
Cellular-based assays	Lymphocyte transformation test
Mediator measurement	uLTE4 for diagnosing AERD
Drug patch tests	Patch test for diltiazem-induced AGEP reaction
Genotyping	HLA-B*15:02 screening for carbamazepine in SE Asians

T cell-mediated endotype

It has been recognized that drug-specific T cells mediate many delayed reactions, and various subclassifications of these delayed hypersensitivity reactions have been proposed [15]. Phenotypic presentations of T cell-mediated reactions are variable and may range from benign exanthems to DRESS. The contribution that T cells have in the pathogenesis of delayed drug reactions is not always clear, and confirmation of their involvement is often mixed. One of the most likely T cell-mediated drug reactions are forms of the baboon syndrome that are caused by systemic drug ingestion with or without prior cutaneous contact allergen exposure. Many cases have very high rates of patch test positivity confirming the delayed-type hypersensitivity pathogenesis [16].

AERD endotype

Aspirin-exacerbated respiratory disease is one of the most well-characterized endotypes in drug allergy. This syndrome affects both the upper and lower airways and is classically characterized by the triad of asthma, nasal polyps, and respiratory reactions to drugs that inhibit cyclooxygenase-1 (COX-1). Exposure to aspirin/NSAIDs does not cause the disease but does lead to acute manifestations. Key features of the pathophysiologic events of AERD include greater respiratory sensitivity and overproduction of cysteinyl leukotrienes, higher expression of the $CysLT_1$ receptor in nasal tissue, overproduction of prostaglandin $(PG)D_2$, and underproduction of PGE_2 (an inhibitor of 5-lipoxygenase) [17, 18]. Platelet-adherent granulocytes also appear to be a rich source of cysteinyl leukotriene production [8••]. Dysregulation of the 5-lipoxygenase-LTC4 synthase pathway leads to eosinophilic tissue infiltration in the upper and lower airways.

HLA-associated drug hypersensitivity endotypes

While pharmacogenetics dates back to the 1950s, precise HLA associations with drug hypersensitivity reactions have been made in the last 15 years [19••]. Numerous HLA associations have been discovered with a variety of drugs, but only a few have had strong enough associations where screening for these haplotypes has been recommended. The HLA-B*15:02 allele has a strong association with carbamazepine-induced SJS in Han Chinese, and screening

for this allele has been shown to be effective in Asian populations [20, 21]. The HLA-B*57:01 allele was discovered in 2002 to be associated with abacavir hypersensitivity syndrome [22]. This is the only drug where a prospective randomized controlled trial of genetic screening for HLA-B*57:01 demonstrated a marked reduction in immunologically confirmed cases of abacavir hypersensitivity [23]. To date, these two alleles are the only ones the FDA recommends genetic screening prior to initiation of therapy of carbamazepine (in Asians) and abacavir [19••].

Biomarkers in drug allergy

Numerous biomarkers have been utilized in drug allergy (Table 3). Few biomarkers have been well validated, and others are not commercially available.

Skin tests

Skin testing with prick and intradermal testing are mainstays of the evaluation of immediate reactions to drugs and has been widely utilized for antibiotics, chemotherapeutics, monoclonal antibodies, perioperative medications, and hormones. Unfortunately, the accuracy of skin testing remains unproven for most medications with its highest yield for penicillin and chemotherapeutics. While a positive skin test is often considered a "gold standard" in drug allergy, sensitization without clinical allergy likely does occur and false-positive skin tests clearly occur with drug skin testing [24, 25].

Specific IgE tests

Commercial and research-based drug-specific IgE assays are available for numerous drugs, and their utility has recently been reviewed by the European Academy of Allergy and Clinical Immunology (EAACI) [26••]. Sensitivity for IgE assays is very modest for beta-lactams and better for neuromuscular blocking agents and platinum-based agents [27]. However, recently, ImmunoCAP testing for chlorhexidine has been shown to have the highest specificity and sensitivity of any drug and, in patients with perioperative anaphylaxis, had a sensitivity of 100% and specificity of 97% [28••].

Basophil activation tests

Basophil activation tests (BAT) are limited by lack of commercial assays with validated results. While the EACCI position statement advocates their use for neuromuscular blocking agents and beta-lactams, the accuracy is inferior to skin tests, especially for beta-lactams [26••]. BAT may have a potential role in quinolone allergy where skin tests are hampered by lack of an agreed-upon nonirritating concentration. The specificity and sensitivity vary depending on the drug with the best results found when ciprofloxacin plus moxifloxacin BAT are utilized in patients suspected of moxifloxacin reactions [29]. Very recently, positive BAT using a research assay to platinum compounds have been found to be associated with more severe initial reactions to platinum chemotherapeutics as well as reactions during rapid drug desensitization [30••]. This group also found that sensitivity was improved with CD203c expression BAT assays (73%) vs. CD63 expression (40%).

Cellular based assays

A number of cell-based assays have been studied in drug allergy with the majority of these assays being research-based with little, widespread, commercial availability. The EACCI position paper has reviewed data for lymphocyte transformation tests, enzyme-linked immunosorbent spot assays, and cell marker and cytokine release assays, and all have received a poor grade C recommendation with modest to low levels of evidence [26••].

Mediator measurement

While serum tryptase is the most widely used mediator assay, it does not lead to precision in the field of drug allergy as it does not differentiate drug-specific reactions from other mast cell activation events. Other mediators have been evaluated in drug allergy, and recently two studies have evaluated the role of measuring urinary (u) LTE4 in patients with AERD [31••]. A retrospective review from Mayo Clinic evaluated the role of uLTE4 in 17 patients with histories of AERD, 11 of whom underwent aspirin challenge with 10 being positive. Urinary LTE4 was measured by liquid chromatography/mass spectrometry and was collected during a 24-h urine collection. A uLTE4 of 241 pg/mg Cr had a sensitivity of 100% and specificity of 92% with a PPV of 42% and a NPV of 100% [31]. A larger study from Poland evaluated 247 patients with AERD (83% with positive aspirin challenges) but used an ELISA-based spot urine collection. While uLTE4 was higher in the AERD group, the test did not yield very useful diagnostic capabilities and clinical history was actually superior. These conflicting results from two separate populations with different assays indicate that further study is needed to clarify the clinical utility of uLTE4 in AERD diagnosis.

Drug patch tests

Drug patch tests may be useful in certain delayed drug reactions with the most consistent results for fixed drug eruptions, AGEP, and baboon syndrome [32]. Patch testing has been shown to be safe in SCAR with a higher rate of positivity for AGEP and DRESS reactions [33••]. The lack of commercially available drug patch tests and standardized testing methodology is still a significant hamper.

Genotyping

As discussed earlier in the "HLA-associated drug hypersensitivity endotypes" section, genotyping for HLA-B*57:01 prior to initiation of abacavir and HLA-B*15:02 prior to carbamazepine in high-risk populations (Han Chinese and Southeast Asian ethnicities) has been endorsed by international guidelines and the US Food and Drug Administration. While genotype screening prior to carbamazepine has been shown to be cost-effective in some studies [34], other studies have shown the cost savings to be offset by increases in phenytoin-related SCAR which are also modestly increased with HLA-B*15:02 [35]. While some authors have proposed pharmacogenetic screening guidelines for phenytoin [36], real-world analysis of extending an HLA-B*15:02 genotype screening approach for phenytoin as well as carbamazepine has not been shown to be cost-effective [35].

Recently, genotyping for HLA-B*58:01 has been shown in a prospective study of Taiwanese patients to reduce the risk of allopurinol-induced SCAR

[37••]. Approximately 20% of individuals screened positive for HLA-B*58:01 and were recommended alternative urate-lowering agents or avoidance. There were no cases of SCAR among 2173 allopurinol users, with an expected incidence of 7 cases. Given the relatively high prevalence of HLA-B*58:01 in this population, the cost-effectiveness of this approach has been questioned. In 2017, a decision-analytical model that incorporated the burden of hypersensitivity derived from real-world data and use of clinical alternatives showed that genotype screening was more cost-effective than no screening with either allopurinol or urate-lowering alternatives [38••]. These results would only apply to populations where the prevalence of HLA-B*58:01 is similar. While pharmacogenetic associations have been made for numerous drug hypersensitivities (including immediate hypersensitivities), data on implementation of screening for these is lacking [19••].

Applications of precision medicine in drug allergy management

By utilizing many of the aforementioned tools including phenotyping, endotyping, and use of biomarkers and drug challenges, management of drug-allergic patients can indeed be more precise (Fig. 1). Recent studies on evaluating different phenotypes of penicillin allergy provide some examples of the use of precision medicine in the management of specific drug hypersensitivity disorders.

Penicillin allergy disease

Penicillin allergy is the most common reported drug allergy in the USA with approximately 10% of the population being labeled as allergic to penicillin. In the past when patients with histories of penicillin allergy were tested, 7–18%

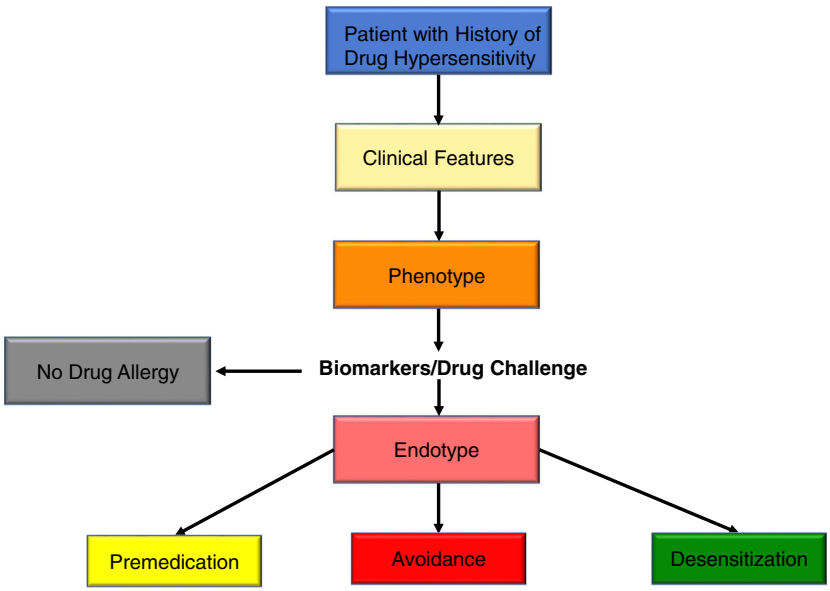

Fig. 1. Current application of precision medicine in drug allergy management.

were found to have positive penicillin skin tests [39, 40]. However, recent studies especially from the USA have shown that the frequency of confirmed penicillin allergy is much lower with a few large studies showing < 2% of patients proven penicillin allergic after amoxicillin challenge [41, 42••, 43•].

Recently, a great deal of attention has been focused on the morbidity associated with a label of penicillin allergy. Many prior studies have indicated the superiority of β-lactams over vancomycin for treatment of susceptible *Staphylococcus aureus* infections and better outcomes for gram-negative bacilli bacteremia [44•]. An important study by Macy and Contreras compared health outcomes in over 50,000 hospitalized patients labeled with penicillin allergy compared to nonallergic controls [45••]. Patients labeled with penicillin allergy were hospitalized longer, treated with significantly more fluoroquinolones, clindamycin, and vancomycin and had more *Clostridium difficile* and methicillin-resistant and vancomycin resistant *enterococcus* compared to those without penicillin allergy. In 2016, the US Centers for Disease Control issued a bulletin to point out the fact that most patients labeled with penicillin allergy are not allergic and that penicillin allergy testing should be part of antibiotic stewardship [46]. Thus, the label of penicillin allergy is a "disease" with associated morbidity.

Precision medicine for hospitalized patients with penicillin allergy

Hospitalized patients frequently require antibiotics and have a higher rate of penicillin allergy than the general population. In recent years utilizing the tools of precision medicine (phenotype and biomarkers), several studies have evaluated actively screening patients for penicillin allergy while hospitalized [42••, 47–49]. These programs have varied regarding who screened patients, who performed testing, and the actual testing protocols. However, all resulted in successful outcomes and showed that only 0–2% had positive skin tests. In addition, some studies showed cost savings and others showed changes in antibiotic use with increased beta-lactam usage. At the author's institution, we have reported on the largest experience with proactive penicillin testing in hospitalized patients [42••]. Our program is a cooperative endeavor between the Department of Pharmacy and the Division of Allergy and Immunology at a large urban public hospital serving and indigent population. The electronic medical record is actively searched to identify all patients who are currently hospitalized and carrying a penicillin allergy label. Patients with acute need of antibiotics and more comorbidities are prioritized. A penicillin allergy questionnaire is utilized to help phenotype patients and determine who is appropriate for testing. The biomarker utilized is immediate penicillin allergy skin testing which, if negative, is then followed by oral amoxicillin challenge. Following this evaluation, patients can then be appropriately reclassified as to their penicillin allergy phenotype. To date, over 400 patients have been tested and 98% have been re-phenotyped as not allergic to penicillin.

Precision medicine for delayed penicillin allergy

Recently, investigators from Israel have evaluated patients with the delayed hypersensitivity penicillin phenotype utilizing the biomarker of immediate penicillin skin testing [50••]. Six hundred forty-two patients underwent immediate skin testing with 5.3% positive and 32% equivocal results. Regardless of

skin test results, all patients underwent graded challenges, in most cases with amoxicillin. Only 1.5% had immediate reactions, 4% had late reactions after the first day, and 6% self-reported mild reactions to a 5-day outpatient challenge. These investigators found that for the delayed hypersensitivity penicillin phenotype, the biomarker of immediate penicillin skin testing was not of any value and recommended that a 5-day oral challenge without skin testing is safe and sufficient to exclude penicillin allergy in this phenotype. This study helps confirm the value of phenotyping and use of appropriate biomarkers in precision medicine for drug allergy.

Conclusion

Principles of precision medicine can currently be applied to management of patients with histories of drug hypersensitivity. Accurate phenotyping of patients is essential to determine which (if any) biomarkers are needed to help confirm or refute a more precise phenotype or endotype. While high-tech innovations such as next generation sequencing have been utilized to define some haplotypes associated with severe drug reactions; low-tech techniques of skin testing remain a mainstay to phenotype and endotype, and help exclude a diagnosis of drug hypersensitivity. In the future, standardization of histories to aid in phenotyping and the development of more precise biomarkers are needed to more effectively manage patients with various drug hypersensitivities.

Compliance with ethical standards

Conflict of interest
The author declares that he has no conflict of interest.

Human and animal rights and informed consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

Trial registration
Not applicable.

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