Controversies in drug allergy: Testing for delayed reactions

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Controversies exist with regard to *in vivo* approaches to delayed immunologically mediated adverse drug reactions, such as exanthem (maculopapular eruption), drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome/toxic epidermal necrolysis, and fixed drug eruptions. In particular, widespread differences exist between regions and practice on the availability and use of intradermal and patch testing, the standard drug concentrations used, the use of additional drugs in intradermal and patch testing to help determine cross-reactivity, the timing of testing in relation to the occurrence of the adverse drug reaction, the use of testing in specific phenotypes, and the use of oral challenge in conjunction with delayed intradermal and patch testing to ascertain drug tolerance. It was noted that there have been advances in the science of delayed T cell–mediated reactions that have shed light on immunopathogenesis and provided a mechanism of preprescription screening in the case of HLA-B*57:01 and abacavir hypersensitivity and HLA-B*15:02 and carbamazepine Stevens-Johnson syndrome/toxic epidermal necrolysis in Southeast Asian subjects. Future directions should include the collaboration of large international networks to develop and standardize *in vivo* diagnostic approaches, such as skin testing and patch testing, combined with *ex vivo* and *in vitro* laboratory approaches. (J Allergy Clin Immunol 2019;143:66-73.)

Key words: *Delayed, intradermal, prick, patch, oral challenge, HLA, acute generalized exanthematous pustulosis, fixed drug eruption, drug reaction with eosinophilia and systemic symptoms, Stevens-Johnson syndrome/toxic epidermal necrolysis*

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Abbreviations used

ADR: Adverse drug reaction
AGEP: Acute generalized exanthematous pustulosis
DRESS: Drug reaction with eosinophilia and systemic symptoms
IDT: Intradermal testing
MPE: Maculopapular drug eruption
SCAR: Severe cutaneous adverse drug reaction
SJS: Stevens-Johnson syndrome
TEN: Toxic epidermal necrolysis

Delayed immunologically mediated adverse drug reactions (ADRs) are defined as those that occur more than 6 hours after dosing,[1] with the exception of acute reactions to chemotherapy, which can occur after 6 hours of treatment in patients premedicated with steroids and antihistamines. Non–life-threatening ADRs, such as delayed exanthem, are common and occur in approximately 5% of treatment courses with drugs such as antibiotics, most typically early in the second week of therapy in the case of new sensitization. Regardless of their specific clinical phenotype, delayed immunologically mediated ADRs are mostly T-cell mediated; this includes the typical morbilliform and urticarial eruptions and more complicated and life-threatening reactions, such as Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and single-organ diseases, such as drug-induced liver and kidney diseases.[1] Although the typical way of classifying T-cell mediated reactions has been the revised Gell-Coombs classification, our knowledge of different models by which drugs activate T cells has advanced considerably over the last 10 years (Fig 1).[2-5] In addition, strong HLA class I associations between severe T-cell mediated reactions, such as abacavir hypersensitivity, SJS/TEN, and DRESS, have led to preprescription screening strategies (Table I).[2,6-16] It is currently not clear the extent to which exanthems are purely caused by parainfectious events to viral or bacterial antigens or stimulation of the immune system by infectious agents with a secondary cutaneous reaction to drugs.[17]

AREAS OF AGREEMENT

Currently, clinical diagnosis is still considered the gold standard for delayed immunologically mediated ADRs but there is general consensus that *in vivo* testing, such as patch testing and/or delayed intradermal testing (IDT), in which sterile preparations of drugs are available, can improve both (1) clinical phenotyping of delayed immunologically mediated ADRs and (2) ascertainment of the causative drug, where the patient is taking multiple drugs started about the same time.[18,19] There is also general agreement that these testing procedures should not be performed for a minimum of 4 to 6 weeks after the acute reaction to avoid both false-positive reactions, false-negative reactions, and flare-ups of systemic reactions, although published evidence to support any of these is weak.[18] For abacavir patch testing, which was also used as a coprimary end point in the HLA-B*57:01 testing licensing trial that confirmed the utility of HLA-B*57:01 as a screening test to prevent patch test–positive abacavir hypersensitivity, patch tests were described as reliably positive as early as 4 weeks after reactions, and no patients experienced a systemic reaction to patch testing.[7,20] Both patch testing and delayed IDT have also been successfully used to look at potential cross-reactivity between structurally related drugs. For IDT in particular, although there is agreement to use the highest nonirritating concentration of drugs, these concentrations have been defined only with regard to immediate reactions. For IDT for many drugs, the highest nonirritating concentration of the sterile intravenous preparation of drug read after 15 to 30 minutes might not be similar to that which evokes a T-cell response after 6 to 24 hours.[21,22] This is particularly true for drugs such as fluoroquinolones and vancomycin, which intrinsically cause direct release of histamine and in which the sensitivity of IDT using the lowest concentrations to avoid non–IgE-mediated mast cell activation by IDT is very poor.[23,24]

CONTROVERSIES AND DIFFERENCES ACROSS REGIONS

The use of IDT and patch testing for diagnosis of delayed immunologically mediated ADRs has been very limited to date in the United States, and there are currently no supportive guidelines in place. This has been driven by a lack of US Food and Drug Administration–approved reagents for testing and a general lack of availability of specialty centers that prepare and compound drugs for IDT and patch testing.[25] The most established experience probably exists in Europe; however, clinics practicing these procedures also exist in North America, Asia, and Australia among others.[20,26-28] There is still a lack of standardized methodological approaches and particularly inconsistency with regard to the drug concentrations (Table II).[22-24,29,30]

For *in vivo* testing, personal and published evidence suggest that IDT is a more sensitive method than patch testing for reactions such as maculopapular drug eruption (MPE) and can be used when sterile soluble forms of the drugs are available.[18,31] Increasing evidence supports the safety of IDT for MPE and DRESS, particularly when 6 or more months has elapsed since the original reaction.[18,32] A questionnaire in 2004 within the European Network in Drug Allergy, the Drug Allergy Interest Group of the European Academy of Allergy and Clinical Immunology, showed differences in performing drug allergy investigations.[31] Guidelines, such as those by the European Society of Contact Dermatitis and the European Academy of Allergy and Clinical Immunology, differ in their recommendations (Table II), making valid comparison of results between centers virtually impossible.[22,29] A position paper providing guidelines on drug concentrations for skin testing was published in 2013, but this article did not differentiate between the nonirritating concentrations used in skin prick testing and IDT for immediate testing versus delayed reactions.[22] This is particularly relevant because IgE-mediated reactions are less dose dependent, and mechanistic studies suggest that the activation of T cells by drug and the subsequent interaction with immune receptors occurs largely in a noncovalent and more dose-dependent fashion.[2] At the present time, there is no consensus on the methodology and interpretation of drug IDT.

The drug concentration and method used and the criteria for positivity of skin test results all influence the sensitivity and specificity of IDT; consequently, thresholds for specific results can vary between different centers. The most reliable delayed skin test is the IDT; however, delayed positive reactions to skin prick tests have been described in patients with DRESS, MPE, and acute generalized exanthematous pustulosis (AGEP), although less frequently.[18] Skin prick testing is carried out on the volar

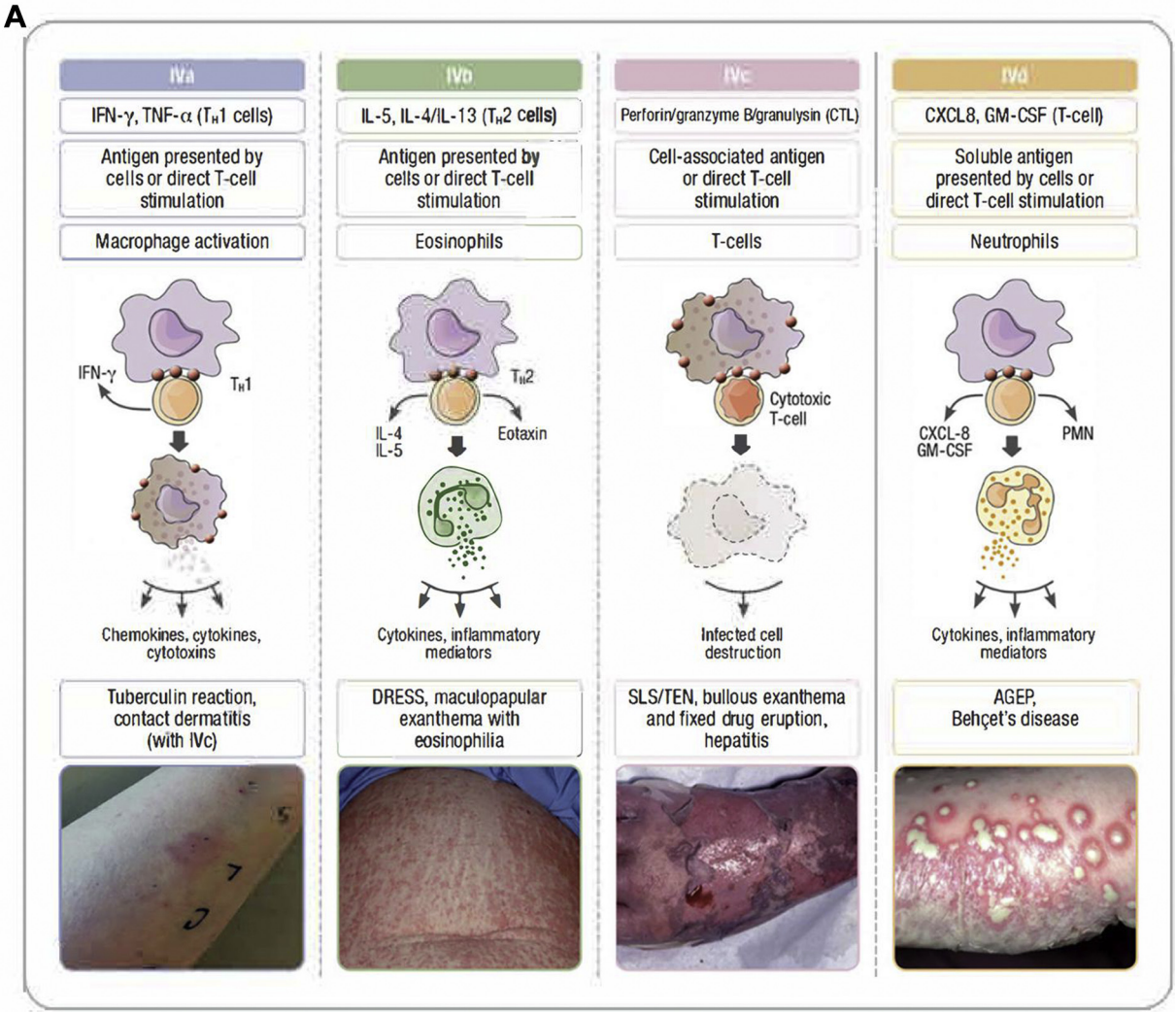

FIG 1. A, Extended Gell & Coombs classification of delayed T cell–mediated ADRs. *CTL*, Cytotoxic T lymphocyte; *PMN*, polymorphonuclear neutrophil. Frames below show representative clinical pictures: *IVa*, positive delayed IDT result to 1% lidocaine in a patient with a contact reaction to lidocaine *[L]* without demonstrable cross-reactivity to mepivacaine *[C]*); *IVb*, maculopapular exanthem; *IVc*, TEN; and *IVd*, AGEP. **B,** Proposed mechanisms of T cell–mediated reactions, including the hapten/prohapten model, the pharmacologic interaction *(p-i)* model, and the altered peptide repertoire model that provide a proposed model for how drugs activate T cells. The hapten-prohapten model shows that the drug covalently binds to a peptide either intracellularly in the endoplastic reticulum before peptide processing and presentation or at the cell surface. The p-i model shows the drug noncovalently binding to the HLA molecule and/or T-cell receptor *(TCR)* to result in direct T-cell activation. The altered peptide repertoire model shows a drug binding noncovalently in the HLA antigen–binding cleft that alters the repertoire of self-peptide ligands, leading to presentation of novel peptide ligands that are recognized as foreign and elicit an immune response.

surface of the forearm by placing a drop of drug product or a small amount of powder, and then the epidermis is perforated with a special lancet.

Approaches to delayed skin testing differ from those of immediate testing for IgE-mediated reactions, where skin prick testing is still commonly used, and results are compared with those obtained with a negative control (0.9% serum saline) and a positive control (histamine). They can be performed with all drugs; however, direct histamine releasers, such as codeine, have to be interpreted with caution. In Europe, for immediate reactions, the recommendation is to perform reading of skin prick tests at 20 minutes, and at this time, the skin prick test response is considered positive if the papule (wheal) is greater than or equal to that measured on the negative control plus 3 mm and if there is a surrounding erythema. A skin prick test has a delayed positive reaction when there is erythema and infiltration at its test location at 24 to 48 hours.[18,33]

For drug patch tests, in Europe the method is fairly standardized, using commercially available patch test chambers appropriate for the type of vehicle. Patch test tapes typically accommodate solid media, such as a drug compound, most commonly dissolved in petrolatum or another vehicle, but

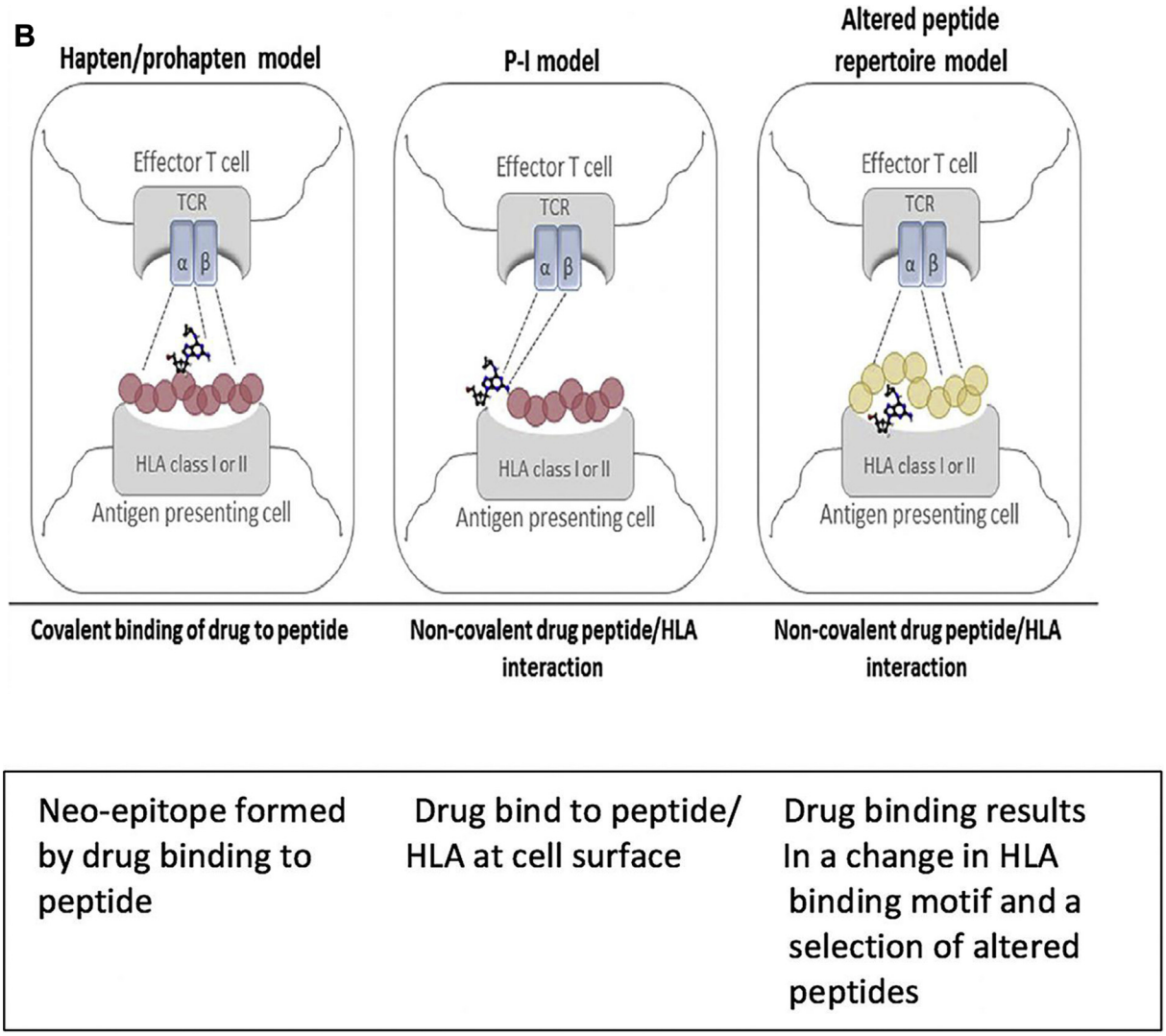

FIG 1. (*Continued*).

occasionally, drugs are mixed with water and have to be applied to either a filter paper disk placed in the patch test well or patch test tape with a built-in filter. Many academic centers and specialized institutions have responsive pharmacy services that can compound drugs to the highest nonirritating concentration. The stability of many patch test materials has not been validated and is most optimally prepared just before testing. It is also possible to use ready-to-use products in which most drugs are diluted at 10% in petrolatum; unfortunately, only a limited number of molecules marketed by Chemotechnique (Velinge, Sweden) are available in some European countries. For certain drugs that are commonly associated with contact reactions, such as corticosteroids and neomycin, commercially available topical preparations of the drugs are used in patch testing. More recently, a method for compounding drugs in the clinic setting by physicians and other providers was described that appeared equivalent to pharmacy-prepared and commercially available patch test reagents in sensitivity and specificity.[34] In most cases, it is necessary to prepare the test material by diluting the drugs in their marketed forms.

For drug patch testing, there are numerous recommendations on the dilutions to be used.[29,30] Two sets of European guidelines have been published for clinicians to conduct drug patch tests with the drug in its commercially available form with each drug diluted to 30%[29] or 20%[30] in petrolatum. Ideally, a concentration of 10% of active ingredient should be obtained. Brajon et al[35] showed that the exact amount of the active ingredient in diluted commercial forms of drugs prepared at 30% in petrolatum varied from 0.05% to 30% and that 25% of the delated patch tests had an active ingredient concentration of less than 2%. Testing the drug "as is" on filter paper chambers for nonirritating drugs might show some promise, but further studies are needed.

Who performs testing also differs widely across geographic regions. Although there is a lack of published evidence, in the United States it is uncommon for allergists, immunologists, or dermatologists to do drug allergy testing by means of either skin prick testing, IDT, or patch testing. This was supported by a recent survey of allergy and immunology program directors in the United States.[25] In Europe dermatologists are more widely available than allergists in many countries and are more likely

TABLE I. HLA associations with delayed immunologically mediated ADR and implications for translation

Drug phenotype	HLA allele	HLA risk allele prevalence	Disease prevalence	OR	NPV	PPV	NNT	Current use as screening test
Abacavir hypersensitivity syndrome[2,7,8]	B*57:01	5% to 8% European ancestry <1% African/Asia 2.5% African American	8% (3% true HSR and 2% to 7% false-positive diagnosis	960	100% for patch test confirmed	55%	13	Routine in HIV clinical practice in developed world
Allopurinol SJS/TEN and DRESS/DIHS[2,9,10]	B*58:01	9% to 11% Han Chinese 1% to 6% European ancestry†	1/250-1/1000	580	100% (Han Chinese, Southeast Asian)*	3%	250	Selectively used‡
Carbamazepine SJS/TEN[2,11]	B*15:02†,§	10% to 15% Han Chinese <1% Koreans, Japanese <0.1% European ancestry	1% to 4% (Han Chinese)	>1000	100% (Han Chinese, East Asian)	3%	1000	Routine in many Southeast Asian countries
Dapsone DRESS/DHIS[2,12]	B*13:01	2% to 20% Chinese 28% Papuans/Australian Aboriginals 0% European/African 1.5% Japanese <2% African and African American	1% to 4% Han Chinese	20	99.8% (Han Chinese, East Asian)	7.8%	84	Screening programs implemented in China and Southeast Asia, where leprosy is prevalent
Flucloxacillin[13]	B*57:01	5% to 8% European ancestry <1% African/Asia 2.5% African American	8.5/100,000	81	99.99	0.14%	13,819	No

NNT, Number needed to test to prevent 1 case of disease; *NPV*, negative predicted value; *PPV*, positive predictive value; *OR*, odds ratio.
*From RegiSCAR data, approximately 60% of Europeans with allopurinol SJS/TEN carry HLA-B*58:01, and HLA risk alleles other than HLA-B*58:01 are thought to be relevant in those of European and African origin.
†HLA-B*15:02 is associated with SJS/TEN in Southeast Asians but not patients with DRESS or MPE. HLA-A*31:01 is more prevalent in European and Japanese subjects associated with carbamazepine DRESS and MPE, and there is prospective evidence for decreased SCARs with HLA-A*31:01 screening in Japanese subjects.[14-16]
‡Might have increased utility in patients at higher risk with renal insufficiency, and because of the high cost of alternatives (febuxostat) and low positive predictive value, adoption has varied.
§Other alleles of the B75 serotype: HLA-B*15:21, HLA-B*15:11, and HLA-B*15:08.

TABLE II. Comparison of international guidelines published for performing delayed IDT

	ESCD[20]	EAACI[21]
Volume injected	0.04 mL (in saline or phenolated saline)	0.02-0.05 mL
Criteria for delayed positivity	Papule at 24 h	24- to 72-h infiltrated erythema
Site	Volar aspect of forearm or extensor aspect of upper arm	Volar aspect of the forearm (or other regions)
Negative control with saline	Yes	Yes
Positive control specific for delayed response	No	No

EAACI, European Academy of Allergy and Clinical Immunology; *ESCD*, European Society of Contact Dermatitis.

to perform both patch testing and, to a lesser extent, delayed IDT.[25]

For both delayed IDT and patch testing, it has been recommended that, when possible, corticosteroids and other immunosuppressants are stopped 1 month before testing. The site of patch testing has most commonly been the upper flat part of the back for pragmatic reasons, although this might be the region with the lowest density of resident T cells, and the relative sensitivity of the back versus other sites for patch testing is unknown.[20,29] The exception is for fixed drug eruptions, in which the sensitivity is very poor unless the patch test is applied at the site of the previous reaction.

The utility and challenges of *ex vivo* assays, such as IFN-γ ELISpot, and *in vitro* assays, such as the lymphocyte transformation test, have been described in detail during the International Drug Allergy Symposium.[36] These tests have many of the same challenges as *in vivo* testing with regard to the need for standardization and validation for different drugs and phenotypes. Their negative predictive value is currently not adequate to justify unsupervised rechallenge with potentially implicated drugs in most settings.[1,37] More recent work suggests that combining laboratory-based *ex vivo* and/or *in vitro* assays with delayed IDT and patch testing might significantly increase the diagnostic sensitivity.[26]

In combination with skin tests, when applicable, oral provocation or challenge tests are still considered the gold standard diagnostic procedure for determination of the culprit drug. For immediate reactions, a single or graded dose challenge is considered adequate to exclude an immediate or IgE-mediated reaction.[38,39] For delayed reactions in the case of a clear history of a documented benign exanthem, a single dose challenge is considered safe.[40] However, in the setting of a more remote

TABLE III. Use of delayed skin prick testing/IDT, patch testing, and systemic provocation for delayed reactions[18,19,32,33]*

	Patch tests†	Prick tests	IDT‡	Systemic provocation
Maculopapular rash	Useful (positive in 10% to 40%)	Potentially useful	Potentially useful, but direct oral provocation might be indicated in low-probability situations	After negative skin test results with delayed readings in low-probability situations; NPV of 90%
Generalized eczema (contact reaction)	Useful	Potentially useful	Potentially useful	After negative delayed skin test result with delayed readings; NPV is unknown
Baboon syndrome or SDRIFE	Useful (positive in 52% to 82%)	Potentially useful	Potentially useful	After negative skin test results with delayed readings; NPV is unknown
Fixed drug eruption	Useful with *in situ* application in area of previous reaction (up to 40% positive)	Unknown	Unknown	At full dose when patch tests or repeated application test results are negative; NPV is unknown
Photosensitization	Photopatch tests with a 5-J exposure to UVA, irradiation at 48 h	No value	No value	No value without exposure to UV
AGEP	Useful; sensitivity depends on the specific implicated drug (up to 58%)	Unknown	Potentially useful	Systemic provocation of suspected drug or cross-reactive drugs is contraindicated
DRESS	Useful (positive in 32% to 64%) dependent on drug Advised 6 mo after disappearance of rash and other sequelae	Described delayed positive at 24 h but unknown utility	Delayed reading at 24 h Currently unknown safety	Systemic provocation with the highly suspected drug and cross-reactive drugs contraindicated
SJS/TEN	Low sensitivity (<30%); can be considered if there is benefit of diagnostic information obtained§	Considered contraindicated	Considered contraindicated	Systemic provocation with suspected drug is contraindicated
Drug-induced liver disease (or another single-organ phenotype)	Low sensitivity if no cutaneous involvement	Low sensitivity if no cutaneous involvement	Low sensitivity if no cutaneous involvement	Systemic provocation with suspected drug is contraindicated

SDRIFE, Symmetrical drug-related intertriginous and flexural exanthema.
*Practices differ significantly between the United States and Europe and parts of Asia at this time. In Europe both allergists and dermatologists perform skin testing, patch testing, and systemic provocation. In the United States allergists perform mainly skin testing and oral provocation, and there are few canters where delayed testing is offered. Drug patch testing and delayed IDT is not frequently offered in the United States by either allergists or dermatologists and is offered in select centers only.
†Initial read at 48 hours; reading occurs at 72 and 96 hours and 1 week if initial result is negative.
‡Read at 48 hours if 24-hour result is negative.
§For allopurinol and its metabolite oxypurinol, patch testing has had 0% sensitivity.

reaction, it might not be adequate to ascertain tolerance of defined daily doses or a full treatment cycle. A single-dose challenge might also be dangerous in the setting of more severe reactions, such as severe cutaneous adverse drug reactions (SCARs), where a single dose has been described to reproduce a reaction particularly in the setting of a more recent reaction. There is a significant lack of consensus for selecting patients who would be appropriate candidates for undergoing oral provocation or challenge after negative delayed IDT or patch testing. For those patients with a history of a mild exanthem and negative delayed patch testing and/or IDT results, it would be common after a tolerated single-dose challenge for the result of a 3-, 5-, or 7-day challenge with an antibiotic, such as amoxicillin, to be negative. Hence the procedure of multiple-day challenge is currently not endorsed, and provocation tests lasting several days with antibiotics are debated currently because of the minimal and theoretical risk of inducing antibiotic resistance or sensitization. Other groups have proposed going straight to oral challenge without the previous skin testing step for these benign reactions.[39] A caveat to this for delayed reactions and particularly those remote in nature is that a single-dose challenge result can be negative, and the reaction might be picked up on the second or subsequent doses only. However, the negative predictive value of provocation tests has been reassuring (>90%) for cutaneous ADRs[41] or β-lactam antibiotic–induced delayed reactions.[42,43] Oral challenge is avoided in the setting of positive IDT or patch test results.

For benign exanthems, there is some evidence to suggest that in the case of an acute exanthem and if the drug (an antibiotic) is still indicated, it can be continued with at least temporary clinical tolerance.[44] For patients with a history of a benign exanthem who have stopped the drug but require it in the future, there is relative consensus among groups for the use of graded reintroduction or a more prolonged desensitization over several hours or days, although the mechanism by which these procedures work is not known. One goal for an international standardization will be to define what a benign delayed exanthem is and under which

circumstances the potential inconvenience and symptoms of the rash outweigh the clinical necessity of drug treatment. SCARs and other severe delayed drug reactions, such as drug-induced liver injury, are generally considered contraindications to rechallenge. In general, if there is an effective alternative drug, the implicated and structurally related drugs should not be reintroduced. Exceptions to this exist in low- and middle-income countries in which diseases of high global burden, such as HIV and tuberculosis, demand complex treatment regimens and in which immunologically mediated ADRs might significantly restrict treatment options.[1] In these cases, where the risk of morbidity and mortality from the underlying disease outweighs or at least equals the risk of morbidity and mortality from the drug reaction, the risk/benefit ratio sways toward sequential rechallenge of potentially implicated drugs. The availability of *in vivo* and *ex vivo* testing to guide rechallenge choices would be extremely helpful in these settings.

Significant knowledge gaps still exist in terms of use of combinations of genetic *in vivo* skin testing and *ex vivo*/*in vitro* diagnostic testing for delayed reactions. Given the lack of 100% negative predictive value of any one diagnostic approach, combined approaches are likely to be necessary. In addition, much like the knowledge gaps that exist in the treatment of SCARs, advances in knowledge of immunopathogenesis will drive the discovery of both therapeutic and diagnostic targets.

CONSENSUS RECOMMENDATIONS AND FUTURE DIRECTIONS

- There is a need for additional evidence and standardization of approaches to the diagnosis of delayed immunologically mediated ADRs in multicenter studies and potential opportunities to incorporate this into treatment intervention studies.
- Standardization of clinical diagnosis is important to studies looking at the efficacy of diagnostic approaches to delayed immunologically mediated ADRs.
- A consensus committee should focus on standardization of procedures for the most common drugs and phenotypes with the highest yield that will have the most clinical effect.
- Current literature supports the use of patch testing and delayed IDT in specific phenotypes (Table III).[18,19,32,33]
- The highest utility of *in vivo* testing approaches will be the combination of exemplary phenotype standardization with *ex vivo* and *in vitro* laboratory-based testing[36]; however, a greater evidence base is needed for not only what combinations of tests to use but when to perform testing after an acute reaction.
- For *in vivo* testing for delayed reactions, in particular for delayed IDT, there is a need for harmonization of approaches, study and standardization of drug concentrations, vehicles, and preparation; and knowledge on stability of test solutions.
- Given the rarity of SCARs, large collaborative networks are needed to study the sensitivity, specificity, and safety of IDT and patch testing in these populations, as well as validating the approach, such as optimal time since reaction to testing, concentration of drugs and/or metabolites, and utility of these approaches, particularly when combined with *ex vivo* and *in vitro* testing in ascertaining the implicated drug, potential cross-reactive drugs, and safe future drug choices.
- Additional scientific advances into the knowledge of immunopathogenesis of these reactions might answer many key questions and will drive strategies for improved prevention, diagnosis, and treatment.

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