



Non-IgE-Mediated Drug Hypersensitivity Reactions

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Abstract

Purpose of Review Non-IgE-mediated drug reactions have traditionally been poorly defined and studied, though they are the most common form of hypersensitivity. Their presentations are highly variable and can range in severity from mild, cutaneous-only reactions to severe systemic disease.

Recent Findings The most notable advance in non-IgE-mediated hypersensitivity reactions is in diagnostics. HLA alleles have traditionally been used for identifying certain patients at risk for abacavir hypersensitivity syndrome, but more recent studies have shown several other HLA alleles associated with severe cutaneous adverse reactions with various medications. This article also highlights the use of delayed intradermal testing for radiocontrast media and patch testing for delayed antibiotic reactions.

Summary Drug reactions remain a major cause of morbidity and reason for treatment changes. Non-IgE-mediated reactions have had an increase in research interest over the past decade with an increased emphasis on better understanding the clinical presentation and underlying pathophysiology.

Keywords Non-IgE-mediated drug allergy · Delayed hypersensitivity reaction · Stevens-Johnson syndrome (SJS) · Toxic epidermal necrolysis (TEN) · Drug reaction with eosinophilia and systemic symptoms (DRESS) · Anaphylactoid

Introduction and Epidemiology

Drug hypersensitivity plays a significant role in a patient's clinical course from effectively prohibiting the use of certain medications as first-line therapies to being a significant cause of morbidity and mortality. While multiple mechanisms exist for hypersensitivity reactions (HSRs), IgE-mediated reactions have been well studied. Conversely, most non-IgE-mediated reactions are poorly understood and can have various clinical phenotypes ranging from immediate-type reactions to significantly delayed presentations. Recent studies have helped better characterize and classify these types of reactions, which will be discussed in this article.

The true incidence of drug-induced HSRs is unknown, as there remains a significant discrepancy between patient-reported and physician-confirmed allergies. Furthermore, earlier studies have concentrated on specific subtypes of drug allergy or select patient groups, which has limited the possibility of generalizing the data to larger populations. More recently, analysis of a large healthcare system highlighted 13.8% of patients reported a drug-induced HSR, with 46.9% of those being of a delayed phenotype (presumably non-IgE-mediated) [1]. In addition, many of the immediate-type reactions in this study may have also been non-IgE-mediated, but it is difficult to differentiate between the two based on the methodology used. Overall, it appears that non-IgE-mediated drug HSRs are at least as common, if not more common, than IgE-mediated reactions, which is consistent with previous findings [2].

While rare at only 0.2% of all drug-related HSRs, severe cutaneous adverse reactions (SCARs) account for a notable portion of the mortality associated with drug allergies [1].

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Proposed Mechanisms for Non-IgE-Mediated Drug Reactions

The Gell and Coombs classification of types I–IV reactions remains a frequently used and relevant scheme, although as our understanding of the immunologic mechanisms of HSRs continues to expand, more exceptions to this system are being identified. While originally proposed in 1963, it has been revised on multiple occasions to include various subtypes based on the underlying immune mechanism [3]. Table 1 summarizes this classification system along with proposed mechanisms of action and frequently encountered examples.

Several notable forms of drug-induced HSRs do not fit well into this classification method including direct mast cell activation, specifically through the Mas-related G protein-coupled receptor-X2 (MRGPRX2), aspirin exacerbated respiratory disease (AERD), and cytokine release syndromes (CRS) which is commonly associated with biologic and cancer therapies. These will be discussed in more detail later in this article.

Recent Advances in Immune Pathogenesis

Sullivan et al. recently showed that IL-22 from antigen-specific T_H22 cells likely contribute to drug-induced HSRs

with drug exposure [4]. Piperacillin-primed T cell clones were analyzed from blood and inflamed skin of piperacillin-allergic patients, and they were stimulated with the drug. T_H1/T_H2 cytokines along with IL-22, IL-13, and interferon- γ (but not IL-17A) were detected which points towards a T_H22 phenotype. In addition, the authors were able to identify aryl hydrocarbon receptor signaling as an essential pathway for drug-specific T_H22 differentiation. Unfortunately, the article did not address what specific drug allergy phenotypes the patients had, and the subjects all carried the diagnosis of cystic fibrosis, which limits the ability to generalize these findings. Nonetheless, additional studies evaluating antigen-specific T_H22 are warranted to better understand its role in HSRs.

Expression of microRNAs (miRNAs), which play a key role in gene expression regulation, have been associated with various non-IgE-mediated HSRs including maculopapular exanthema (MPE), SJS, and TEN. Monroy-Arreola et al. recently showed an upregulation of miRNA-18a, miRNA-21, and miRNA-155 from peripheral blood mononuclear cells after drug-specific stimulation in patients with known delayed reactions [5]. The group postulated that miRNA-155 may potentially be used as an early biomarker for delayed HSRs, although additional studies are needed to confirm these findings.

Table 1 Immunologic mechanisms as defined by the Gell and Coombs classification system[3]

Classification	Immunologic mechanism	Clinical presentations
Type I	• Mast cell- and basophil-mediated • IgE dependent or independent	Anaphylaxis, urticaria, angioedema, bronchial hyperreactivity, rhinitis, emesis, hypotension
Type IIa	• Antibody-mediated (IgG or IgM) • Opsonization and phagocytosis via complement activation	Autoimmune hemolytic anemia, immune thrombocytopenic purpura
Type IIb	• Antibody-mediated (IgG or IgM) • Complement- and Fc receptor-mediated neutrophilic inflammation	Goodpasture syndrome, pemphigus vulgaris
Type IIc	• Antibody-mediated cellular dysfunction (stimulation or inhibition)	Graves' disease, myasthenia gravis
Type III	• Immune complex-mediated tissue injury • Recruitment and activation of innate immune cells (neutrophils)	Arthus reaction, serum sickness
Type IVa	• T_H1 cell-mediated • Macrophage activation and release of IFN-γ and TNF-α	Allergic contact dermatitis, tuberculin reaction
Type IVb	• T_H2 cell-mediated • Eosinophilic inflammation	Maculopapular exanthema, DRESS
Type IVc	• CD8+ cytotoxic T cell-mediated • Perforin/granzyme B involvement or through Fas-ligand dependent pathway	SJS/TEN
Type IVd	• Drug specific T cell-mediated (produces IL-8 and GM-CSF) • Sterile neutrophilic inflammation through neutrophil chemotaxis and inhibition of cellular apoptosis	AGEP

IgG immunoglobulin G, *IgM* immunoglobulin M, *T_{H1}* T helper cell type 1, *T_{H2}* T helper cell type 2, *IFN- γ* interferon- γ , *TNF- α* tissue necrosis factor- α , *DRESS* drug reaction with eosinophilia and systemic symptoms, *SJS* Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis, *IL-8* interleukin-8, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *AGEP* acute generalized exanthematous pustulosis

Mas-Related G Protein-Coupled Receptor-X2

McNeil et al. first described the role of MRGPRX2 in pseudoallergic reactions in 2015 and noted its ability to recognize a variety of endogenous and exogenous stimuli [6]. In addition to being expressed in MC_{TC} cutaneous mast cells, it is also found in sensory neurons and keratinocytes. While independent of drug-specific IgE, its activation leads to a very similar, yet slightly more transient, phenotype as IgE-mediated reactions. Over the past 5 years, several drugs have been identified that use MRGPRX2 to directly activate mast cells including vancomycin (vancomycin flushing syndrome), many neuromuscular blocking agents (with the exception of succinylcholine), fluoroquinolones, icatibant, and morphine. Single nucleotide polymorphisms in MRGPRX2 may predispose individuals to HSRs through this receptor which may eventually play a significant role in predicting non-IgE-mediated responses to these frequently used medications [7,•].

Approach to Evaluating Non-IgE-Mediated Drug Reactions

Non-IgE-mediated drug-induced HSRs are commonly encountered but often difficult to appropriately identify and manage due to the limited diagnostic tools available. The clinical history remains the most important element when evaluating for these types of HSRs as it will help determine which diagnostic tests may be helpful and assist in guiding management options. The authors' approach to these situations is outlined below.

Differentiating IgE-Mediated and Non-IgE-Mediated Reactions

Classically, drug allergies were categorized as immediate-type or delayed-type, with IgE-mediated reactions being associated with the onset of symptoms within 1 h of drug exposure. This stringent criterion is likely misleading as there is significant cross-over with delayed IgE-mediated reactions and more immediate non-IgE-mediated reactions [8]. IgE-mediated HSRs have been noted to occur up to 6 h after exposure [9]. The more useful differentiating factors include the symptomatology, specific properties of the drug, and what treatments best managed the episode. Skin (skin prick, intradermal, and patch) and in vitro testing have been shown to be helpful in specific instances, but robust data is lacking for the evaluation of most medication allergies other than penicillin.

Clinical Presentation

The clinical presentation of non-IgE-mediated HSRs can be highly variable, ranging from benign exanthems to severe

disseminated disease. The timing of these reactions can also vary from immediate-type reactions, such as IgG-mediated anaphylaxis, to symptoms beginning weeks after the initiation of therapy. Table 2 summarizes the key clinical features for the more commonly seen HSRs.

Diagnostic Testing

Diagnostic testing is not warranted in most cases as the clinical history alone is often indicative of a non-IgE-mediated HSR. In specific situations, testing may be helpful. One such example is when multiple medications were used in a short period, and the culprit drug is unclear. Another instance is in patients that may require a similar medication to one that previously led to a non-IgE-mediated reaction. This has been shown to be a useful strategy for delayed maculopapular rashes and fixed drug eruptions associated with contrast media [18].

Unfortunately, the validity of available testing methods is not consistent across the different types of non-IgE-mediated HSRs or between drugs themselves (Table 2). The sensitivity and specificity for patch, delayed intradermal, and in vitro/ex vivo testing is unknown for the vast majority of drugs. Therefore, interpretation can be exceedingly difficult and may lead to inappropriate management decisions. The gold standard remains an observed challenge in situations where there is diagnostic uncertainty, and the benefits of the challenge outweigh any potential risks. This will be discussed further under the management section.

Patch Testing

Patch testing (PT) is a tremendously useful and reliable tool in the evaluation of allergic contact dermatitis to topical drugs [19]. However, its usefulness for other non-IgE-mediated drug-induced reactions is less clear. Furthermore, the methodology for drug PT has not been properly evaluated for the vast majority of drugs including establishing the correct drug concentrations, vehicles, and duration of occlusion, which further limits its utility [11]. Commercially available PT kits to select antibiotics, NSAIDs, and anticonvulsants are available in Europe but are difficult to obtain in the USA. PT remains a valid tool in select situations where it may provide clarity in the identification of the offending agent (Table 2).

The optimal timing of PT has not been established, but expert opinion is that it should be performed at least 6 weeks after the reaction in question [13••]. A longer timeline of at least 6 months is preferred but not always possible. As systemic immunosuppressive agents including corticosteroids can alter PT results, it is generally recommended that patients have discontinued the agent at least 1 month prior to PT. Rapid withdrawal of these suppressive agents can lead to

Table 2 Types of non-IgE-mediated hypersensitivity reactions [1, 10–17]

	Clinical presentation	Time to symptom onset	Proposed mechanism of action	Diagnostic testing to identify culprit drug	Commonly implicated drugs
Non-IgE-mediated anaphylaxis					
IgG-mediated anaphylaxis	Urticaria, angioedema, vomiting, hypotension, dyspnea, and anaphylaxis. Indistinguishable from IgE-mediated anaphylaxis	Minutes to hours	Macrophage and basophil activation through FcγRIII; release of PAF. Large quantities of antigen are needed	BAT but availability in the U.S. is limited	None proven but possibly omalizumab, infliximab, and NMBAs
MRGPRX2	Urticaria, angioedema, vomiting, hypotension, dyspnea, and anaphylaxis	Immediate (typically faster than IgE-mediated process)	Direct activation of mast cells and basophils through MRGPRX2; results in degranulation (histamine, leukotrienes, prostaglandins)	None commercially available	Vancomycin (Vancomycin Flushing Syndrome), NMBAs, fluoroquinolones, icaftibant, leuprolide, and morphine
Anaphylatoxins (complement activation)	Urticaria, angioedema, hypothermia, vomiting, hypotension and anaphylaxis. Thought to work synergistically with other mechanisms of anaphylaxis	Minutes to hours	Complement activation leads to the release of C3a, C5a, and C5b-C9 which activates mast cells, basophils, endothelial cells, and smooth muscles	SC5b-9 level (terminal complement complex)	Not proven but possibly heparin and liposomal drug infusions (polyethylene glycol)
Cytokine release syndrome	Fatigue, headache, pruritus, dyspnea, flushing, hypotension, and vomiting. More common with first dose of medication	Minutes to hours	Immune activation of monocytes/macrophages and T/B cells; rapid release of proinflammatory cytokines (IL-6, IL-10 and IFN-γ)	No validated tests	Biologics (rituximab, obinutuzumab, alemtuzumab, brentuximab), ATG and tisagenlecleucel
Severe cutaneous adverse reactions (SCARs)					
Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN)	Detachment of necrotic epidermis involving both skin and mucosal surfaces; SJS ≤ 10%; SJS/TEN overlap 10%–30%; TEN ≥ 30%	4–28 days	CD8 + T cell- and NK cell-mediated release of cytotoxic mediators including granulysin	B*58:01 allopurinol; B*15:02 carbamazepine. Little utility for PT other than for carbamazepine	Allopurinol, antiepileptics (carbamazepine, lamotrigine, phenytoin), sulfonamide antibiotics, and NSAIDs
Drug eosinophilia and systemic symptoms (DRESS)	Fever, lymphadenopathy, peripheral eosinophilia, extensive rash, facial edema, organ involvement	2–8 weeks	Unknown but likely due to T _H 2-mediated release of proinflammatory cytokines and eosinophil recruitment	B*58:01 allopurinol; A*32:01 vancomycin; B*13:01 dapsone. Some utility in PT and IDT for antibiotics but limited sensitivity	Antiepileptics (phenobarbital, carbamazepine, phenytoin), allopurinol, sulfonamide antibiotics, and dapsone
Acute generalized exanthematous pustulosis (AGEP)	Hundreds of sterile pustules on erythematous base with no to minimal mucosal involvement; frequently febrile	Hours to days (longer for certain drugs)	Drug-specific CD4 + and CD8 + T cells activation leading to apoptosis of keratinocytes via INF-γ and CM-CSF secretion	PT and IDT have both shown reasonable utility in diagnosis, especially for β-lactam antibiotics	Antibiotics (β-lactam, quinolones, sulfonamide), hydroxychloroquine, and azole antifungals
Predominantly cutaneous HSRs					

Table 2 (continued)

	Clinical presentation	Time to symptom onset	Proposed mechanism of action	Diagnostic testing to identify culprit drug	Commonly implicated drugs
Maculopapular eruption (MPE)	Morbilloform rash, predominantly on the trunk. No systemic symptoms	3–12 days (earlier with re-exposure)	T _H 2 cell-mediated inflammation with eosinophilic infiltration	Possible utility for PT and IDT although low sensitivity for most drugs	Antibiotics (β-lactam, sulfonamide, fluoroquinolone, tetracycline)
Fixed drug eruption (FDE)	Erythematous/violaceous annular patch, plaque, or bullae with a dusky-grey center which occurs at the same site with re-exposure	Days to weeks (earlier with re-exposure)	Drug-specific CD8 + T cell activation leading to IFN-γ release and damage to melanocytes and keratinocytes	PT at a hyperpigmented site of previous FDE lesion. May be helpful for NSAID-induced FDE	Antibiotics (β-lactam, sulfonamide, fluoroquinolone), triazoles, and NSAIDs
Allergic contact dermatitis (ACD)	Eczematous lesions with vesicles and bullae	Days to weeks	T _H 1 cell-mediated activation of macrophages and release of IFN-γ and TNF-α	Both PT and IDT have high utility; can be used effectively in most cases	Topical antibiotics and NSAIDs
Erythema multiforme (EM)	Fixed target-like lesions, typically symmetric on extensor surfaces of extremities. ≤ 10% of cases are due to drug hypersensitivity	Days to weeks	CD4 + and CD8 + cell activation resulting in keratinocyte necrosis from TNF-α, perforin, and granzyme B release	Limited data on PT and IDT; unclear if helpful	NSAIDs, antiepileptics (barbiturates, carbamazepine), and antibiotics (sulfonamide, β-lactam, macrolides, nitrofurantoin)
Erythema nodosum (EN)	Erythematous, painful nodules (panniculitis) frequently located on shins. ≤ 10% of cases are due to drug hypersensitivity	Hours to days	Immune-complex deposition in deep dermis and adipose tissue venules with initial neutrophilic inflammation	None available to determine culprit drug	Antibiotics (tetracycline, β-lactam, sulfonamide) and oral contraceptive
Systemic drug-related intertriginous and flexural exanthema (SDRIFE)	Symmetric, well-demarcated gluteal/perianal erythema and involvement of ≥ 1 other intertriginous location	Hours to days	Unknown but most likely CD4 + and CD8 + T cell involvement with associated macrophage activation and direct cytotoxicity	PT and IDT may have utility but notably limited sensitivity	β-lactam antibiotics, RCM, pseudoephedrine, and mitomycin
Drug-induced autoimmune bullous eruptions	Multiple types including bullous pemphigoid, linear IgA dermatosis, and pemphigus	Days	Various mechanisms depending on subtype; most probably due to T cell dysregulation leading to autoantibody formation	Limited data on PT, IDT, and in vitro testing	Vancomycin (linear IgA bullous disease), ACE inhibitors, furosemide, TNF-α inhibitors, β-lactam antibiotics, and NSAIDs
Lichenoid drug eruption	Erythematous or violaceous patches or plaques; frequently in photodistributed pattern	Weeks to months	Unknown but likely CD4 + and CD8 + T cell-mediated process	PT may have some utility. IDT has not been evaluated	ACE inhibitors, thiazide diuretics, statins, and TNF-α inhibitors

Table 2 (continued)

Clinical presentation	Time to symptom onset	Proposed mechanism of action	Diagnostic testing to identify culprit drug	Commonly implicated drugs
Subacute cutaneous drug-induced lupus erythematosus (SACLE) and chronic cutaneous (CCLE)	Months to years	Unknown but multiple theories including production of autoreactive T/B cells and NETosis CCLE: classic discoid skin lesions in photosensitive areas	SACLE: ANA + > 80%; anti-histone + > 33%; anti-Ro/SSA + > 80%; anti-La/SSB + > 45%	SACLE: Antihypertensives (calcium channel blockers, thiazide diuretics), terbinafine, PPI/CCLE: fluorouracil agents, NSAIDs, and pantoprazole
Systemic HSRs				
Serum sickness	1–2 weeks	Fever, pruritic rash, arthralgias, uveitis, and lymphadenopathy	Immune complex deposition in tissue (preferentially joints), activating complement and phagocytes	Antivenom, ATG, and biologics (rituximab, infliximab, omalizumab)
Serum sickness-like reaction (SSLR)	4–10 days	Arthralgias, lymphadenopathy, urticarial rash, and +/– fever. Typically milder than classic serum sickness	Unknown but possibly due to direct toxic effect of drug metabolites on cells (cefaclor)	Antibiotics (β-lactam, sulfonamide, tetracycline), antiepileptics
Drug-induced pneumonitis	Days to years	Cough, pulmonary edema, bronchospasm, and fibrosis. May have fever and weight loss	Various immune-mediated and metabolic mechanisms	Methotrexate, nitrofurantoin, immune checkpoint inhibitors, and taxanes
Drug-induced interstitial nephritis	2–4 weeks	Acute kidney injury, eosinophiluria, white cell casts; rash may be present	Various immune-mediated and metabolic mechanisms	NSAIDs, antibiotics (β-lactam, sulfonamide, fluoroquinolone) and PPI
Drug-induced liver disease (DILI)	Typically ≤ 3 months	Hepatocellular, cholestatic or mixed injury. May have rash and/or fever	Various immune-mediated and metabolic mechanisms	Acetaminophen, antibiotics (β-lactam, sulfonamide), and NSAIDs
Systemic drug-induced lupus erythematosus (DILE)	Months to years	Diffuse discoid lupus-like lesions with systemic manifestations (fever, serositis, arthralgia)	Unknown but multiple theories including production of autoreactive T/B cells and NETosis	Hydralazine, procainamide, isoniazid, hydrochlorothiazide, PPIs, TNF-α inhibitors, and IVIG/SCIG

PAF platelet-activating factor, BAT basophil activating test, NMBA neuromuscular blocking agent, MRGPRX2 mas-related G protein-coupled receptor-X2, IFN-γ interferon-γ, ATG anti-thymocyte globulin, NSAID nonsteroidal anti-inflammatory drugs, ACE angiotensin-converting enzyme, PPI proton pump inhibitor, NETs neutrophil extracellular traps, ANA antinuclear antibody, RNP ribonucleoprotein antibody, ENA extractable nuclear antigen antibodies, IVIG intravenous immunoglobulin, SCIG subcutaneous immunoglobulin

relapse of more severe forms of non-IgE-mediated reactions and should be done cautiously if PT is indicated.

In patients with fixed drug eruptions (FDEs), especially to nonsteroidal anti-inflammatory drugs (NSAIDs), patch testing has acceptable specificity, although the data is limited [11]. The patch must be placed on hyperpigmented sites where a previous FDE lesion occurred as it is dependent on drug-specific, resident memory CD8 + T cells, which is only present in affected skin. When lesions are no longer visible, the reliability of the testing is poor.

The sensitivity of PT for systemic drug-related intertriginous and flexural exanthema (SDRIFE) and abacavir hypersensitivity syndrome is acceptable, but is considerably less so for other non-IgE-mediated reactions. PT has very little utility in SJS/TEN, except for certain antiepileptic drugs such as carbamazepine [20].

The authors' practices utilize patch testing in very select situations, understanding that delabeling is typically not possible with a negative test due to the poor sensitivity for nearly all types of non-IgE-mediated HSRs.

Delayed Intradermal Testing

Over the past several years, there has been a renewed interest in delayed intradermal testing (IDT) with several small, yet promising, studies showing a possible utility for this diagnostic method. Standardization is being attempted across Europe and should provide more clear testing guidelines in the coming years [21]. Similar to PT, IDT is typically performed 4 to 6 weeks after the acute reaction and patients should be off systemic immunosuppression for at least 1 month [22]. Despite initial concerns that IDT may lead to reactivation of the HSR, recent studies have shown a good overall safety profile although rare occurrences have been reported [23–25]. IDT appears to have better sensitivity than PT in several instances including antibiotic-related MPEs and DRESS [26]. It also has utility in ADRs to chemotherapeutics, analgesics, proton pump inhibitors, and NSAIDs [27, 28].

Recently, several studies have highlighted the use of IDT for evaluating iodinated radiocontrast media (RCM)-related delayed reactions [29]. Trautmann et al. evaluated 13 patients with a history of a delayed-type HSR (11 with MPE, 1 with systemic hypersensitivity syndrome, 1 with FDE) and had positive IDT in all cases to the incriminating RCM [30••]. They also performed IDT on various other RCM, and subsequently, the patients were able to tolerate an intravenous challenge to a non-sensitized RCM. This ability to identify alternate RCMs in truly sensitized patients may be a very practical clinical use for delayed IDT. Our practices have adopted the more regular use of IDT for RCM in recent years for this situation.

Due to the lack of a reference standard and the ethical implications of challenging patients with positive IDT, the

precise sensitivity and specificity of IDT remains unknown. In addition, the appropriate concentrations for testing are not well established, and generally, the non-irritating concentrations for immediate-type reactions are used. This, however, may significantly reduce the sensitivity of testing and additional studies are needed to evaluate this position [13••]. Finally, as expected, IDT appears only to be a meaningful tool for T cell-mediated process and not for all types of non-IgE-mediated reactions.

Genetic Testing (HLA)

Testing for specific human leukocyte antigen (HLA) alleles has become standard of care for the evaluation of specific non-IgE-mediated HSRs, and this practice will likely continue to increase as more associations are identified. Lehloeny et al. summarizes the present understanding of these associations along with negative and positive predictive values (NPV and PPV) in table format [13••]. The most prominent example is the current recommendation for routine screening of B*57:01 prior to the initiation of abacavir to reduce the risk of hypersensitivity episodes [31].

Other associations including HLA-A30 B13 Cw6 haplotype with FDEs to trimethoprim-sulfamethoxazole, B*58:01 with allopurinol-associated SJS/TEN and DRESS, and A*32:01 with vancomycin-induced DRESS [32–34]. Overall, HLA testing has excellent NPV but low PPV, which may support its use to identify the offending agent in situations where multiple medications were used concurrently prior to the development of a HSR.

Other Testing Methods

Several in vitro and ex vivo techniques are being investigated in the research setting but are not commercially available at this time. This includes lymphocyte transformation test, enzyme linked ImmunoSpot (ELISpot), and flow cytometry to evaluate for activated T cell populations [13••]. While these do show some promise as complementary testing to a detailed history and skin testing, their lack of availability for clinical practice will limit their utility in the coming years. ELISpot specifically is frequently used for research purposes. A discussion of these methods is beyond the scope of this article.

Management of Non-IgE Hypersensitivity

Acute management of non-IgE-mediated reactions is dependent on both the specific subtype and severity of the HSR. For most occurrences, elimination and strict avoidance of the offending agent is the primary course of action. This is often the only step necessary, as symptoms are frequently

self-limiting after the offending agent is removed. For more severe non-IgE-mediated HSR, additional interventions may be indicated and are discussed below.

Subsequent avoidance of drugs, and potentially any cross-reactive drugs, associated with severe non-IgE-mediated reactions remains the mainstay of long-term management. For milder reactions, delabeling can be considered in the appropriate clinical setting after testing (if available) and/or drug challenge. This remains a reasonable option when the benefits of using the specific drug in question outweighs potential risk. The authors of this article routinely perform challenges in patients with histories consistent with MPEs and occasionally for FDEs (unless consistent with generalized bullous FDE).

Alternative Therapy and Cross-Reactivity

In patients with suspected non-IgE-mediated drug-induced HSRs, alternative therapies should always be considered if a similar efficacy and safety profile exists. However, in situations where a related medication is the best possible option, cross-reactivity remains an important concern. The vast majority of data on cross-reactivity comes from the antibiotic (mainly β -lactams) and RCM literature, and it is wholly dependent on skin testing to determine sensitivity, which was discussed earlier in this article as an imperfect tool for diagnosing non-IgE-mediated HSRs [29, 35]. As challenges are not routinely performed in patients with positive PT or IDT during evaluation, the true cross-reactivity of nearly all drugs is not known.

Using PT and IDT as an indicator for sensitivity, the cross-reactivity between aminopenicillins and aminoccephalosporins ranges from 17% to 37% [36–38]. This supports the notion that cross-reactivity between β -lactams is likely dependent on having the same or similar R1-side chains, analogous to IgE-mediated reactions. IDT has shown promising results when used to demonstrate tolerance to other β -lactams (cephalosporins, carbapenems, and monobactams) in patients with a T cell-mediated HSR to penicillins. Cross-reactivity rates with cephalosporins have generally been <3% in these situations and even lower for carbapenems [39, 40].

Conversely, in a recent study by Trubiano et al., the authors demonstrated high cross-reactivity between penicillins [26]. Of the 32 patients that had suspected severe T cell-mediated hypersensitivity to a penicillin, 44% had negative IDT to all reagents while 50% had positive testing to at least 1 additional penicillin (other than the suspected culprit drug). Ninety-two percent of the patients challenged with a first- or second-generation cephalosporin passed. While IDT had poor sensitivity in this study, it did suggest that

avoidance of all penicillins is likely the appropriate step in this situation.

Vancomycin remains the second most commonly implicated antibiotic with DRESS, but data addressing cross-reactivity with other glycopeptides is limited. One recent study used a combination of IDT and ELISpot to determine 13% cross-reactivity in 15 patients with HLA-A*32:01-related vancomycin-induced DRESS [41].

In regards to antiepileptic drugs, cross-reactivity between aromatic antiepileptics has been established for over a decade [42]. However, a small study by De Luca et al. suggested nonaromatic antiepileptic drugs and benzodiazepines were well tolerated in this population [43].

Drug Challenges

Drug challenges remain the diagnostic gold standard for non-IgE-mediated HSRs when the benefits of using the potentially offending agent outweigh the possible risks. This is particularly true for mild-to-moderate reactions but can also be considered in more severe subtypes in very select cases, only if safe and efficacious alternatives are not available. As discussed earlier, the sensitivity and specificity of skin testing remains largely unknown for these reactions; therefore, drug challenges are an essential tool to determine tolerance. In addition, certain drugs such as antibiotics are often urgently needed which does not provide time for delayed reads on skin testing.

There remains a debate on the required duration of challenges for delayed HSRs. Recent reports have supported the use of single-dose challenges instead of prolonged challenges as very little value was added with the additional days of therapy [44, 45•]. The authors support the use of one- or two-dose challenges in most situations of delayed HSRs, especially for mild-to-moderate reactions. Conversely, a prolonged challenge with 1/10th of the dose followed by the remaining 9/10th a week later is a reasonable approach for patients with a possible history of more severe reactions.

Rechallenging for benign nonimmediate HSRs should also be considered. A small study of 18 children with previously positive drug challenges showed that 16 (89%) of them were able to tolerate the culprit drug upon rechallenge after a 3-year avoidance interval, suggesting a natural tolerance acquisition in pediatric patients [46].

In rare circumstances where no therapeutic options exist and lack of treatment may lead to mortality, drug challenges have been used in patients with SCAR. Lehloeny et al. have reported on challenges in HIV patients with SJS to antituberculosis medications where no other treatment options exist [47]. In 6 such patients, they showed that methylprednisolone when used within 100–200 min of a rechallenge reaction prevented development of SCAR [48••].

“Treating Through”

“Treating through” is the common practice of continuing a drug despite an objective reaction. While substantial anecdotal evidence exists, very little is noted in the published literature. A recent retrospective study of 18 patients with a MPE to antibiotic therapy was evaluated for the possibility to remain on therapy with supportive care [49]. Of these, 12 (67%) were able to stay on therapy with improvement of their skin symptoms and underlying infection at the time of discharge. The authors recommend this approach in patients that can be closely monitored from a clinical and laboratory standpoint. This can generally be done with regular communication with a patient’s provider and checking peripheral eosinophil counts along with organ-specific markers including liver, renal, and cardiac function when applicable.

Desensitization

Desensitization remains a vital option for patients with a history of drug-induced type I hypersensitivity (both IgE- and non-IgE-mediated) that require the culprit drug as first line therapy. The underlying mechanism is not fully understood for IgE-mediated processes, and even less is known for IgG-mediated hypersensitivity. A recent murine study suggested that desensitization is possible for anaphylactic reactions that involve stimulatory IgG receptors, but we are not aware of any published human cases [50].

Desensitization for severe non-IgE-mediated HSRs is not recommended due to the potential life-threatening nature of these events. However, for mild to moderate reactions such as MPEs, desensitization has been suggested as a method to obtain tolerance. How desensitization can occur for delayed HSRs is unclear, and the true efficacy of these procedures remains controversial. The vast majority of the available data on this topic is from studies on sulfonamide antibiotics, especially in the HIV population.

Sulfonamide Antibiotics

Well over 20 protocols have been proposed for sulfonamide antibiotic desensitization, which all have been equally effective [51, 52]. Nonetheless, there remains controversy on the necessity of desensitization versus a single-dose or 2-dose challenge. Three randomized trials to date have shown similar efficacy between challenges and desensitization at a 1–2-week follow up period; however, the largest study by Leoung et al. showed a significantly higher percentage of patients remaining on trimethoprim-sulfamethoxazole (TMP-SMX) that underwent desensitization (80%) compared to the full-dose challenge group (62.8%) [53–55]. It should be noted

that the frequency of rash between the two groups was no different, and the main reason for discontinuation included frequent headaches and fevers.

A more recent study further highlights the safety and efficacy of direct challenges to TMP-SMX in both HIV and non-HIV populations for nonsevere reactions [56••]. One-hundred and ninety-one out of 204 (94%) patients tolerated either a single-dose or 2-step challenge. Furthermore, in patients with an unspecified sulfonamide allergy, 98.9% successfully completed the procedure.

The authors recommend a full dose rechallenge in patients with either nonsevere immediate reactions or benign MPEs to sulfonamides as an efficient, safe, and effective approach based on the available evidence.

Chemotherapeutic and Biologic Agents

Hypersensitivity reactions to chemotherapeutic and biologic agents are quite common and will be discussed later in this article. Desensitization to platins, taxanes, and monoclonal antibodies are frequently practiced at large medical centers that specialize in these procedures [57, 58]. Rapid desensitization has been very effective for both type I hypersensitivity and moderate to severe infusion reactions with an excellent safety profile [59]. A recent analysis comparing patients requiring rapid desensitization for first-line oxaliplatin therapy due to previous HSRs versus a control group of nonallergic patients receiving the same therapy showed similar survival data [60]. This suggests that if indicated as the preferred agent by the practicing oncologist, rapid desensitization to these drugs should strongly be considered to optimize outcomes for the patient.

Premedication Protocols

Premedication is often used for RCM-related immediate HSRs as well as for biologic and chemotherapeutic agents. Treatment with antihistamines, leukotriene antagonists, and systemic steroids have shown to be helpful in reducing mild-to-moderate symptoms, especially for infusion-related reactions. The recent anaphylaxis practice parameter update from the Joint Task Force on Practice Parameters (JTFPP) did recommend premedication to prevent index hypersensitivity/infusion reactions to chemotherapy, although the certainty rating of evidence was very low [61]. In the same guidelines, the committee did not recommend routine premedication to prevent recurrent HSRs to RCM if a different low- or iso-osmolar agent was being used. Differentiation of the index RCM-related reaction is important as premedication may still have a role in severe, cutaneous T cell-mediated reactions [62].

Types of Non-IgE-Mediated Drug Allergies

Many forms of non-IgE-mediated drug reactions exist, each with its unique pathophysiology and clinical characteristics. Table 2 contains the most common forms of these hypersensitivity reactions along with their clinical presentation, time to symptom onset, proposed mechanism of action, available diagnostic testing, and a brief list of commonly implicated drugs.

Non-IgE-Mediated Anaphylaxis

Traditionally, anaphylaxis has been categorized as an exclusively IgE-facilitated process; however, the understanding of alternate pathways has grown with several proposed mechanisms (Table 2). These generally fall into two IgE-independent pathways including mast cell/basophil-mediated and non-mast cell/basophil-mediated [63, 64]. Those involving activation of mast cells and basophils occur through crosslinking of Fc γ receptors by specific IgG, G protein-coupled receptors (e.g., MRGPRX2), or modulation of the kinin system. Other mechanisms such as the activation of the complement system through anaphylatoxins (C3a, C5a, and C5b-9) and release of platelet activating factor (PAF) have effects on numerous cells, which can lead to a clinical phenotype consistent with anaphylaxis [65]. Many other mechanisms have been proposed but additional research is needed to confirm these pathways.

Severe Cutaneous Adverse Reactions (SCARs)

SCARs encompass a range of delayed hypersensitivity reactions with drug reacting T cells being the integral component. These reactions can occur during the initial exposure to the drug or on subsequent encounters. Table 2 outlines the 3 major drug allergies within SCAR which include Stevens-Johnson Syndrome/Toxic epidermal necrolysis (SJS/TEN), drug eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP). Due to the severity of these reactions including a mortality of up to 40% in patients with TEN, early recognition and management is essential along with an accurate diagnosis to reduce the risk of future exposure [66].

Genetic risk factors with SCARs were discussed earlier in this article with certain HLA alleles having been linked with drug-specific SCARs. The strongest of which is the association between HLA-B*57:01 and abacavir hypersensitivity syndrome. Non-genetic factors have also been identified including both drug and host factors. Specific drugs have higher rates of SCARs such as carbamazepine and other anti-epileptics, allopurinol, and antimicrobial agents. The risk of SCAR increases with higher doses of the culprit drug [67]. Host-related factors include underlying malignancy, systemic lupus erythematosus, or infections (e.g.,

tuberculosis and HIV). Of note, individuals with detectable HIV levels have a 1000-fold increased risk for SCAR [68].

Specific Drug Considerations

Biologic Agents

The safety of biologic agents (BAs) has come into focus due to their increased use in clinical practice. BAs are unique in their ability to directly modify the immune system which has led to expected and unexpected adverse reactions (ARs). These include infusion reactions, autoimmunity, secondary immunodeficiencies, cytokine release syndrome, and hypersensitivity reactions (both IgE-mediated and non-IgE-mediated). A distinct classification system has been proposed for BAs to encompass the many types of AEs observed in clinical practice [69]. This section will primarily focus on non-IgE-mediated hypersensitivity reactions.

Both immediate and delayed hypersensitivity has been well documented, although the mechanism of these non-IgE-mediated reactions remains poorly understood. Proposed pathways include IgG-mediated mast cell activation through Fc γ RIII, complement activation and mast cell stimulation through MRGPRX2, and cytokine release [70]. Diagnostic testing is limited currently for non-IgE-mediated reactions; therefore, the diagnosis is made strictly by clinical history or provocation challenges. Fortunately, most of these IgE-independent reactions are managed by reducing the infusion rate and adequate pretreatment with antihistamines, leukotriene modifying agents, and systemic steroids. Hypersensitivity reactions have been reported for many biologics, but the most common culprits include infliximab (anti-TNF- α), trastuzumab (anti-HER2), rituximab (anti-CD20), omalizumab (anti-IgE), basiliximab (anti-IL-2R α), and cetuximab (anti-EGFR) [69].

Traditional Chemotherapeutic Drugs

A wide variety of hypersensitivity reactions have been documented in cancer patients undergoing therapy with traditional chemotherapeutic agents. Many agents present with a mixed phenotype that may fall in multiple subtypes based on the classic types I–IV classification system. For example, oxaliplatin may have immediate type I symptoms with urticaria and hypotension but also develop delayed cytokine storm-related symptoms [71]. While the vast majority of concern for platinum-based drugs and taxanes are with IgE-mediated reactions, SJS/TEN and DRESS have also been recognized to occur [72].

Desensitization has been well described as a management consideration in those with both non-IgE-mediated type I and type IV reactions without features of SJS/TEN. It is generally reserved in those patients in whom alternative therapy is limited or associated with worse clinical outcomes.

The proposed mechanism for desensitization in type I reactions is through the induction of inhibitory pathways of mast cells and basophils with the administration of small incremental doses of the culprit drug [72]. Conversely, the mechanism for desensitization for type IV reactions is less clear, and the efficacy of this approach is less established.

Radiocontrast Media

A variety of hypersensitivity reactions have been reported to the most commonly used nonionic RCM with a prevalence between 0.7 and 3% [73]. Interestingly, IgE-mediated reactions have likely been severely underreported in the past and are now being more thoroughly evaluated in the clinical setting. Several non-IgE-mediated pathways have been proposed for both immediate- and non-immediate-type reactions. Direct activation of mast cells via the MRGPRX2 receptor may occur with iohexol but studies have shown mixed results and additional research is needed in this area [74, 75]. Skin biopsy results from cutaneous lesions of both immediate- and delayed-type reactions have shown T-cell infiltrate in the dermis with predominant CD4 + T cells [76]. Direct complement activation has also been theorized as a mechanism [73].

The role of intradermal skin testing for the evaluation of non-IgE-mediated reactions and premedications were discussed earlier in this chapter.

Conclusion

Non-IgE-mediated mechanisms make up the majority of drug hypersensitivity reactions but remain poorly understood due to their various presentations, range of severity, and limited diagnostic methods. There have been significant advances in genetic testing of HLA alleles which has provided a notable approach in predicting certain types of SCARs, and newer diagnostic tools are being investigated which have shown early potential. Observed drug challenges remain the gold standard and should be part of the practicing allergists' toolbox. Finally, there remain significant unmet needs for non-IgE-mediated reactions including more reliable diagnostic tests, standardized premedication protocols, and validated treatment algorithms.

Compliance with Ethics Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

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.

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