Old dog begging for new tricks: current practices and future directions in the diagnosis of delayed antimicrobial hypersensitivity

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Purpose of review
Antimicrobials are a leading cause of severe T cell-mediated adverse drug reactions (ADRs). The purpose of this review is to address the current understanding of antimicrobial cross-reactivity and the ready availability of and evidence for in-vitro, in-vivo, and ex-vivo diagnostics for T cell-mediated ADRs.

Recent findings
Recent literature has evaluated the efficacy of traditional antibiotic allergy management, including patch testing, skin prick testing, intradermal testing, and oral challenge. Although patch and intradermal testing are specific for the diagnosis of immune-mediated ADRs, they suffer from drug-specific limitations in sensitivity. The use of ex-vivo diagnostics, especially enzyme-linked immunospot, has been highlighted as a promising new approach to assigning causality. Knowledge of true rates of antimicrobial cross-reactivity aids empirical antibiotic choice in the setting of previous immune-mediated ADRs.

Summary
In an era of increasing antimicrobial resistance and use of broad-spectrum antimicrobial therapy, ensuring patients are assigned the correct 'allergy label' is essential. Re-exposure to implicated antimicrobials, especially in the setting of severe adverse cutaneous reaction, is associated with significant morbidity and mortality. The process through which an antibiotic label gets assigned, acted on and maintained is still imprecise. Predicting T cell-mediated ADRs via personalized approaches, including human leukocyte antigen-typing, may pave future pathways to safer antimicrobial prescribing guidelines.

Keywords
antibiotic allergy, enzyme-linked immunospot, hypersensitivity, lymphocyte transformation test, patch testing, severe cutaneous adverse reactions

INTRODUCTION

T cell-mediated drug hypersensitivities are a group of immune-mediated adverse drug reactions (ADRs) of varying phenotype and severity. Descriptions of antimicrobial-associated T cell-mediated ADRs date back to the use of the first sulfa antimicrobials [1] and then almost a decade later to early preparations of penicillins [2,3]. These immune-mediated ADRs result in antimicrobial allergy 'labels' that impact patient outcomes and antimicrobial usage [4▪▪,5,6▪▪]. For the diagnosis of antimicrobial allergy, the use of skin prick testing and intradermal testing (SPT/IDT) remains the mainstay of first-stage diagnosis for immediate reactions suspected to be IgE-mediated. This should be followed by an ingestion challenge which, in combination with SPT/IDT, is still considered to be the gold standard [7]. However, in the setting of serious T cell-mediated ADRs, both patch testing, a more established test for the diagnosis of delayed reactions, and SPT/IDT lack the

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KEY POINTS

- Antimicrobials are a leading cause of T cell-mediated ADRs.
- The antimicrobials primarily associated with T cell-mediated ADRs include glycopeptides, sulfonamides, β-lactams, antiretrovirals, and hepatitis C antivirals.
- An understanding of drug latency and allergy 'phenotypes' can aid drug causality assessment.
- Although patch testing and IDT are specific in the diagnosis of T cell-mediated ADRs, they suffer from drug-specific limitations in sensitivity and when negative they can never be used as the sole basis for rechallenge.
- A knowledge of side chain cross-reactivity aids empirical antibiotic choice in the setting of immune-mediated ADRs.
- The use of ex-vivo diagnostics, especially ELISpot, presents promising new approaches to assigning causality in antimicrobial-associated T cell-mediated ADRs.
- An understanding of cytokine outputs specific to each phenotype will aid the development of these tools in the future.
- Predicting T cell-mediated ADRs via personalized approaches, including HLA-typing, may pave future pathways to safer antimicrobial prescribing.

100% negative predictive value (NPV) necessary to rechallenge patients to drugs either orally or systemically following negative testing [8]. In this review, we will address the current understanding of antimicrobial cross-reactivity and the ready availability of and evidence for immune-mediated ADR in-vitro, in-vivo and ex-vivo diagnostics.

The epidemiology of serious T cell-mediated reactions varies according to the region studied and is driven by genetic predisposition to these reactions. In general, given the high prevalence of antibiotic use, 50% or more of severe cutaneous adverse reactions (SCARs) globally are associated with antimicrobials – commonly penicillins, glycopeptides, and sulfonamide antibiotics – and antiretrovirals [5,9▪▪,10▪▪]. The most serious of these reactions include Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustolosis (AGEP). Additionally, abacavir, a guanosine analog nucleoside reverse transcriptase inhibitor, is associated with a severe human leukocyte antigen (HLA)-B*57:01-restricted, $CD8^+$ T cell-mediated hypersensitivity reaction [abacavir hypersensitivity syndrome (AHS)], which is characterized clinically by fever, malaise, gastrointestinal symptoms, and late onset of rash (70%) a median of 8 days after initiation of dosing. In the setting of multiple implicated antimicrobials, the cause of SCARs and other immune-mediated ADRs is often unclear despite application of published causality assessments [11,12].

EFFECTOR IMMUNOLOGY OF T CELL-MEDIATED ADVERSE DRUG REACTIONS

Immune-mediated ADRs can be classified by the revised Gell and Coombs classification (Table 1) [13]. This review focuses on type IV, T cell-dependent immune-mediated ADRs. The pathogenesis of T cell-mediated immune responses has been long debated, yet the presence of allergen-specific T lymphocytes is an observation in most drug-allergy reactions. White *et al.* [4▪▪] reviewed the current mechanistic hypotheses of T cell-dependent immune-mediated ADRs namely pharmacological interaction of drugs with immune receptors (the p-i concept), the hapten/prohapten model, and the altered peptide repertoire model (Fig. 1). The cellular and cytokine response within immune-mediated ADRs vary (Table 1).

Many of the SCARs are known to rely on drug-specific T-cell responses that can persist in the circulation for more than 20 years after drug exposure [60]. Blistering and severe immune-mediated ADRs (SJS/TEN or AHS) are thought to correlate with $CD8^+$ T-cell infiltration, whereas simple exanthema and DRESS are largely associated with $CD4^+$ T cells or mixtures of $CD4^+$ and $CD8^+$ T cells [61,62]. In general, cytokines upregulated in immune-mediated ADRs are IL-2, IL-5, IL-13, and IFNγ [63]. The key immune mediators differ slightly for each immune-mediated ADR phenotype, summarized in Table 1. An understanding of immune mediators is vital for future works measuring cytokines in ex-vivo T-cell diagnostics.

HISTORICAL APPROACHES TO T CELL-MEDIATED HYPERSENSITIVITIES

Testing for immune-mediated ADRs remains problematic because of both lack of widespread availability and low sensitivity of conventional methods. Many patients with nonspecific rashes or those that occur during the course of an acute infection will not demonstrate reproducible symptoms on future rechallenge. Caubet *et al.* [64] demonstrated that only 6.8% of patients with a history of antibiotic associated 'rash' had a reproducible phenotype on oral challenge. In recent studies, IDT has been suggested to be more sensitive than patch testing

Table 1. T cell-mediated adverse drug reaction classification, pathogenesis, and phenotype guide

Type IV ADR	Cellular mediators	Cytokine mediators	Phenotype	Specific immunological parameters for phenotype
Type IVa	Primary: Th1	IFNγ	Contact dermatitis	Contact dermatitis – primarily $CD8^+$ T-cell infiltrate. ↑ IFNγ, TNFα, IL-18. Also noted ↑ IL-31, IL-6 in serum and IL-33, IL-9, IL-4 in skin [14–18]
	Secondary: macrophages	TNFα	Tuberculin reactions	
		IL-18		
Type IVb	Primary: Th2	IL-4	MPE[b]	MPE – $CD4^+$ more than $CD8^+$ T cells. Acute episodes Th1 predominate, ↑ IL-12, IFNγ/TNFβ in blood, CXCL9/CXCL10 skin. ↓ IL-17 compared with SJS/TEN. ↑ Th2/IL-5 later explains pruritis [19–24]
	Secondary: B cells, IgE, IgG4, mast cells, eosinophils	IL-5 IL-13	HSS DRESS	DRESS – ↑ TNFα, IFNγ, and IL-2 production, production correlates with disease severity. Activation-regulated chemokine (TARC/CCL17) drive Th2 responses, higher than observed in SJS/TEN. Skin biopsies noted eosinophils in 20%; whereas $CD8^+$ T cells and granzyme B (+) lymphocytes ↑ in severe disease [25▪,26,27]
Type IVc	Primary: cytotoxic T cells	Granzyme B	SJS	SJS/TEN – $CD8^+$ T-cells and NK cells lead to keratinocyte apoptosis. Granulysin specific to SJS/TEN. ↑ IL-10 and T_{reg} associated with resolution of TEN/SJS. T_{reg} function often impaired. ↑ IL-2, IL5, IL6, IL-17, and CCL27 in plasma/blister fluid. Th17 cells also have a role [23,28–35]
		Perforin	TEN	Linear IgA disease – Often mistaken for TEN, however, characteristic linear IgA deposits are evident on direct immunofluorescence studies. ↑ $CD4^+$ T-cell, neutrophils and eosinophilis. Mixed Th1/Th2 cytokine response. ↑ IL-2, IL-4, IL-5 and IL-8 noted [36–41]
		Fas ligand	Linear IgA disease	FDE – ↑ Intraepidermal $CD8^+$ T cells, ↑ IFNγ, cytotoxic granules, granzyme B and perforin. ↑ $CD8^+$ T cells, $CD4^+$ T cells and neutrophils cause tissue damage. Late ↑ IL-10 and T_{reg} ($CD4^+CD25^+Foxp3^+$) control immune reaction, however, IL-15 secreted by keratinocytes continues to propagate $CD8^+$ T cell-mediated injury [42,43]
		Granulysin	DILI[c] [a]FDE [a]EM	EM – ↑ IL-2, IL-6, IL-8, IL-17A, IFNγ. ↑ Th1/$CD4^+$ T-cell infiltrate with IL-17 expression. ↓ IL-10, noted. At skin level, ↑ $CD4^+$ T cell with IL-17 (Th2) expressing cells. $CD8^+$ T cells noted within epidermis, and $CD4^+$ T cells are noted in dermis. Variations in T-cell/cytokine expression if the stimulant is HSV or drug induced (e.g., higher $CD8^+$ T cells and TNFα in drug-induced EM) [44–46]
Type IVd	Primary: Th1/Th17	GM-CSF		
	Secondary: neutrophils	IL-8 CXCL8	AGEP	AGEP – ↑ $CD4^+$ T cells infiltrate, $CD8^+$ T cells and ↑ ↑ CXCL8 and GM-CSF. CXCL8 is involved in the chemotaxis of neutrophils; Th17 cells involved [47–50]

ADR, adverse drug reaction; AGEP, acute generalized exanthematous pustolosis; DHR, drug hypersensitivity reaction; DILI, drug-induced liver injury; DRESS, drug reaction with eosinophilia and systemic symptoms; EM, erythema multiforme; FDE, fixed drug eruption; GM-CSF, granulocyte monocyte colony-stimulating factor; HSS, hypersensitivity syndrome; MPE, maculopapular exanthema; ND, no data; NK, natural killer; PMN, polymorphonuclear cell; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; T_{reg}, regulatory T cell.

[a]Not classically described by Gell and Coombs criteria of T cell-mediated hypersensitivity.

[b]MPE, otherwise known as 'morbilliform' drug eruption, is the most commonly reported antibiotic-associated T cell-mediated ADR.

[c]DILI – DILI will not be covered in detail in this review, as the mechanism can be dose dependent/predictable or unpredictable. The unpredictable reactions may in fact be immune-mediated or metabolic in origin. T lymphocytes secreting granzyme B have been noted on liver biopsy. $CD4^+/CD8^+$ T cells secreting IL-13 and IFNγ have been detected in serum from in patients with DILI. The most commonly implicated antimicrobials are amoxicillin-clavulanate and flucloxacillin, in particular in those with HLA-B*57:01.

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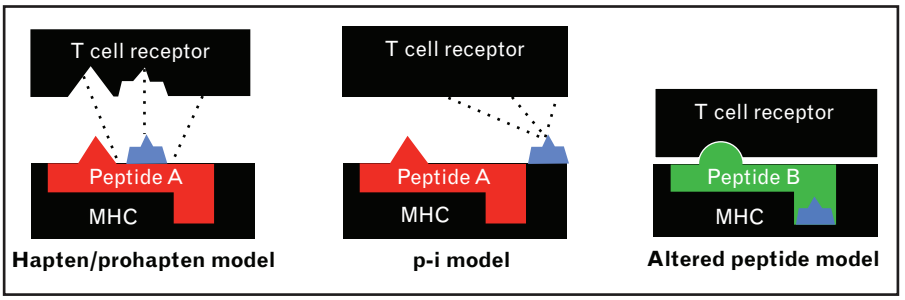

FIGURE 1. Schematic of proposed T cell-mediated ADR pathogenesis theories. The hapten/prohapten model is where an antigen (e.g. antibiotic) covalently binds to a self-peptide, is intracellularly processed and then presented with MHC to T cells as a 'foreign antigen' [51,52]. An example of the hapten/prohapten model is when penicillin G derivatives bind lysine residues on serum albumin [53–55]. The p-i concept (the pharmacological interaction with immune receptor) is based upon noncovalent binding of antigens to HLA or T-cell receptor without immune processing, explaining how reactions can occur upon first presentation [51,56]. The 'altered self-repertoire model' is based upon drug models (e.g. abacavir) that demonstrated that drugs can occupy positions in the peptide-binding groove of the MHC, altering the binding cleft and subsequently the specificity of MHC binding [57–59]. ADR, adverse drug reaction; HLA, human leukocyte antigen; MHC, major histocompatibility complex. Reproduced with permission from [51–59].

for T cell-mediated ADRs. However, in the setting of serious T cell-mediated ADRs, patch testing is still considered 'safer' than delayed-SPT/IDT [65,66]. The details of patch testing and IDT for T cell-mediated ADRs are described below and a summary of T cell-mediated ADRs is provided in Table 2.

Patch testing

The specificity of patch testing for SCARs has been high in settings where drug concentrations have been validated against negative controls. The sensitivity of patch testing varies, however, and is highest for DRESS (32–80%) [112,113] and AGEP (58–64%) [112,114], and lowest for SJS/TEN (9–24%) [112,114] and maculopapular examthem (MPE) (10–40%) [65,113]. Patch testing lacks an appropriate positive control and results may be difficult to interpret in patients who are on immunosuppressants that impact T cell-mediated immunity. For antibiotics, patch testing to the upper back is generally recommended 6 weeks to 6 months after skin healing [115]. In a multicenter study of patch testing in SCARs, Barbaud *et al.* [112] demonstrated that patch testings were most frequently positive for β-lactams (primarily amoxicillin) and pristinamycin. Buonomo *et al.* [116] demonstrated patch testing's utility in immune-mediated ADRs, predominately cephalosporin-associated MPE, in a retrospective cohort. Barbaud *et al.* [66] utilized patch testing in 29 cases of pristinamycin-associated immune-mediated ADRs, with a higher than expected sensitivity noted (69%). In 27 patients with oral challenge confirmed fixed drug eruption (FDE) to trimethoprim-sulfamethoxazole (TMP-SMX), 93% sensitivity for patch testing was demonstrated [117]. However, in a recent study by Andrade *et al.* [118] 0% (0/15) of FDE were positive on patch testing. The utility of patch testing in immune-mediated ADRs caused by quinolones and TMP-SMX is notoriously poor [112,119,120]. Patch testing has been demonstrated to be effective in a small number of antibiotic-associated SJS/TEN [114,121–123], AGEP [70,112,120,124,125], FDE [126–128], DRESS [112,129], MPE [130], and erythema multiforme [131] case series. To date, success with patch testing in cases of suspected antiretroviral hypersensitivity has been limited to abacavir. Patch testing for abacavir showed 100% specificity and 87% diagnostic sensitivity when used as an adjunctive test to define true AHS [8,132].

SUMMARY AND RECOMMENDATIONS

(1) A positive patch testing has high specificity for specific antibiotic-associated immune-mediated ADRs and appears most useful for DRESS more than AGEP and of lessor utility for FDE, MPE, and SJS/TEN.
(2) A negative patch testing does not exclude a drug-specific immune-mediated ADR and should never be used as the sole basis for rechallenge of the implicated antibiotic(s).

Delayed intradermal testing

The use of delayed-IDT (0.02–0.05 ml of highest nonirritating concentration of antimicrobial applied to volar forearm skin, then read at 48–72 h [133]) is recommended in the investigation of T cell-mediated ADRs [134,135]. Similar to patch testing, delayed-IDT is limited by the significantly less than 100%

Table 2. Summary of antimicrobial associated T cell-mediated adverse drug reactions

Characteristics	SJS/TEN	DRESS	AGEP	EM	FDE	Drug-induced linear IgA	MPE
Drug latency (days)	4–28[a]	14–42	1–18[b]	<1–10	<1–14[c]	1–18[d]	4–9
Prodrome	Common	Common	Uncommon – fever with acute phase	Uncommon – unless severe	Uncommon	Uncommon	Uncommon
Distinguishing cutaneous features	Starts face → thorax	Morbilliform ± follicular accentuation	Starts face → thorax	Can involve all regions	Can involve all regions. Commonly lips, genitalia, perianal area, hands, feet	Sub-epidermal blisters on trunk, extensor surfaces, buttocks and face (especially perioral region)	Morbilliform eruption – macules, papules or rarely pustules/ bullae. Desquamation often follows resolution
	Palms, soles and scalp rarely involved	Usually >50% BSA involvement and >2 of facial edema (50% cases); infiltrated lesions; scaling; or purpura	Dozens to hundreds nonfollicular, sterile, pin-sized pustules, generally with background erythema. Flexural accentuation	Symmetrical target lesions, spreading in centripetal fashion	Well demarcated ± vesiculation or blistering		
	Nikolsky sign[e]			Oral involvement can be isolated finding			
Mucosal involvement	Yes (very common – 90%)	Yes (infrequent)	Yes (uncommon, only lips)	Yes (common – 70%)	Yes (infrequent)	Yes (common – 80%)	No
Commonly implicated antibiotics	β-lactams (penicillins >cephalosporins), vancomycin, sulfonamides, macrolides, quinolones, tetracycline, clindamycin	Sulfonamides, vancomycin, minocycline, dapsone >> β-lactams, pristinamycin nevirapine, telaprevir, acyclovir	Vancomcyin[f], amoxycillin, ciprofloxacin, gentamicin, carbapenems[g]	Sulfonamides, penicillins, quinolones[h]	Sulfonamides, tetracyclines, penicillins, quinolones, macrolides, metronidazole	Vancomycin >>amoxycillin, amoxicillin-clavulanate quinolones, sulfonamides	β-lactams, (especially penicillin, amoxicillin/amoxicillin-clavulanate), sulfonamides, cephalosporins, lincosamides
Scoring algorithms[i]	ALDEN [11]	RegiSCAR [67]	EuroSCAR [68]	Nil	Nil	Nil	Nil
Preferred diagnostics (*in vitro*)	PT	PT>	PT	PT	PT>	PT	Delayed-DT
		Delayed-IDT			Delayed-IDT[j]		
Research diagnostics (*ex vivo*)	LTT	LTT	LTT	LTT	LTT	LTT	LTT
	ELISpot	ELISpot	ELISpot	ELISpot	ELISpot	ELISpot	ELISpot

AGEP, acute generalized exanthematous pustolosis; BSA, body surface area; DRESS, drug reaction with eosinophilia and systemic symptoms; ELISpot, enzyme-linked immunospot assay; EM, erythema multiforme; FDE, fixed drug eruption; HSV, herpes simplex virus; IDT, intradermal testing; Linear IgA, linear immunoglobulin IgA disease; LTT, lymphocyte transformation test; MPE, maculopapular examthem; ND, no data; PT, patch testing; SJS, Stevens–Johnson Syndrome; T cell-mediated adverse drug reactions, delayed hypersensitivity reactions; TEN, toxic epidermal necrolysis; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Much shorter duration for antibiotics than other drugs (1 versus 11).

[b]Can be as early as 48 h on drug reexposure, median time 14 days.

[c]Can be as short as 30 min to 8 h after drug administration [69].

[d]Latency periods are rarely up to 30 days.

[e]Nikolsky sign – the ability to extend the area of sloughing with the application of gentle lateral pressure on seemingly unaffected skin. Asboe- Hansen sign ('bullae spread') – lateral extension of bullae with gentle pressure.

[f]Vancomycin most commonly implicated antibiotic.

[g]Rare reports secondary to carbapenems (meropenem, doripenem, ertapenem) [70,71].

[h]Infective causes are more common in EM than SJS (e.g., HSV1 and mycoplasma).

[i]In cases where a specific scoring system has not been developed, 'Naranjo score' can be employed as a guide [72].

[j]At the site of previously described reaction.

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sensitivity and lack of a suitable positive control [136]. Recommendations for IDT vary regionally and there is a lack of evidence-based volumes and reagents (β-lactam versus non-β-lactam) [121,133–135]. IDT has predominately been utilized for β-lactam antimicrobials, especially penicillins more than cephalosporins, in patients with a history of non-SJS/TEN T cell-mediated ADR [122,123,137]. A positive result involves dermal induration/erythema at injection site, which will significantly exceed 5 mm from baseline, 24–72 h after testing. Although extension of the local dermal response at the skin testing site is uncommon, IDT is generally not recommended for the assessment of SJS/TEN [123,138], because of risk of systemic events. Adverse reactions following delayed IDT for non-SJS/TEN ADRs are rarely reported [139–141], primarily occur in the setting of immediate testing [142–144] and are often related to errors in concentrations and/or volumes used.

Alternative guidelines do not specify the same 'contraindications' to IDT, however, suggest performing IDT only after a negative patch testing [145]. Although it appears patch testing is preferred over IDT for FDE [118], the sensitivity of IDT for other T cell-mediated ADRs appears higher than that observed with patch testing [64,130,141,146,147]. In a study of patients with suspected reactions to β-lactams ($n = 235$ MPE), 7% (18/235) had a positive delayed-IDT, whereas 8.5% (20/235) with negative IDT demonstrated a positive result with oral challenge [147]. IDT has also been used less frequently for other antimicrobials associated with immune-mediated ADRs, such as metronidazole [148]. Limitations include only antimicrobials in a commercially available and sterile injectable form can be utilized, short-lived local histamine release (e.g., ciprofloxacin and vancomycin) and irritation (e.g., flucloxacillin) of some products, and overall low NPV. The sensitivity of delayed-IDT from a mixture of small studies has been reported as 6.6–36.3% for MPE (higher with penicillins more than cephalosporins) [149–151] and 64–100% for DRESS [113,137].

SUMMARY AND RECOMMENDATIONS

(1) Delayed-IDT can be employed as a first-line investigation for non-SJS/TEN immune-mediated ADRs, although the highest nonirritating concentrations for delayed testing have not been validated for most drugs.
(2) A positive delayed-IDT result is highly suggestive of an immune-mediated ADR, but a negative delayed IDT does not exclude an immune-mediated ADR and should never be used as the sole basis for rechallenge.

Direct oral challenge

Since first-stage tests such as patch testing and IDT do not have 100% NPVs, oral challenge is contraindicated in certain SCARs (e.g., SJS/TEN/DRESS) [8,152] and AHS. Oral challenge is required to confirm immune-mediated ADRs following negative delayed-IDT or patch testing in the remaining phenotypes [150,153▪▪]. For the investigation of delayed reactions, a prolonged oral challenge (5–7 versus 3 days) increases sensitivity [150,154]. Owing to the low rate of positives obtained from isolated delayed IDT or patch testing [153▪▪,155–157], and the high rate of Type A ADRs clouding 'labels' [6▪▪], a move toward direct oral challenge has been proposed, especially for 'low-risk' phenotypes [6▪▪,158]. This is particularly true in children where viral infections or drug–infection interactions are prevalent. Direct oral rechallenge in a cohort of patients with a history of MPE demonstrated only a 6.9% adverse event rate (compared with 3.5% prior) [159▪]. A direct 5-day oral rechallenge in 119 pediatric patients with mild antibiotic-associated MPE elicited a 5.4% positive response rate, but no serious reactions occurred [80]. The safety of oral rechallenge for antiretroviral immune-mediated ADRs has not been established, but guidelines advise that patients with mild to moderate rash without constitutional symptoms can continue antiretrovirals with close clinical monitoring. In these cases, symptoms should be managed with antihistamines and topical corticosteroids. Physicians commonly 'treat through' mild ADRs to nonnucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine or efavirenz, hepatitis C drugs such as telaprevir and antibiotics such as β-lactams and sulfa antimicrobials [160,161]. Desensitization protocols exist for hypersensitivity reactions to the antiretrovirals tipranavir [162], amprenavir [163], darunavir [164], efavirenz [165], and have been tried with nevirapine [166].

RECOMMENDATIONS

(1) Direct oral challenge for 5–7 days should be employed after a negative patch testing or delayed-IDT in the setting of mild to moderate antibiotic skin rashes without evidence of fever, mucosal involvement, malaise, or internal organ involvement.
(2) Oral challenge with a suspected drug should never be employed in the setting of SJS/TEN or DRESS.
(3) Ideally, an observed oral or ingestion challenge in the setting of required antibiotic therapy should be employed following negative IDT/

Table 3. Empirical antimicrobial therapy recommendations in the setting of T cell-mediated adverse drug reaction (non-SCAR) where in-vivo and ex-vivo testing is not available

Antimicrobial allergy 'label'	Antimicrobials to avoid in the setting of known T cell-mediated ADR history
Penicillin V/G	Cephalothin
	Cefoxitin
Aminopenicillins	Ampicillin/amoxicillin
	Cefaclor[a]
	Cephalexin[a]
Antistaphylococcal penicillin	Penicillin V/G
	Flucloxacillin/dicloxacillin/oxacillin
	Piperacillin-tazobactam
	Ticarcillin-clavulanate
First-generation cephalosporins[b]	Amoxicillin[c]
	Cefaclor[d]
Second-generation cephalosporins	Ceftriaxone[e]
	Cefotaxime[e]
	Cefepime[e]
	Cephalexin[f]
Third-generation cephalosporins	Cefepime[g]
	Cephalothin[h]
	Cefuroxime[g]
	Cefotaxime[g]
Fourth-generation cephalosporins	Aztreonam[i]
	Cefitraxone[i]
	Cefuroxime[i]
	Cefotaxime[i]
Carbapenems	Carbapenems
Monobactams	Ceftazadime[k]
Antibiotic sulfonamides	Nil

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ADR, adverse drug reaction; SCAR, severe cutaneous adverse reactions: Stevens–Johnson syndrome, toxic epidermal necrolysis; drug reaction with eosinophilia and systemic symptoms; acute generalized exanthematous pustolosis.
[a]Avoid if amoxicillin/ampicillin delayed immune-mediated ADR because of shared/similar R1 side chain.
[b]If cefazolin is the implicated antimicrobial, this is generally an isolated reaction because of the absence of shared side chains and, therefore, other β-lactams could be employed for non-SCAR phenotypes.
[c]If cephalexin allergy then avoid amoxicillin/ampicillin because of shared/similar R1 side chain.
[d]Avoid if cephalexin allergy because of shared/similar R1 side chain.
[e]Avoid if cefuroxime allergy because of shared/similar R1 side chain.
[f]Avoid if cefaclor allergy, because of shared/similar R1 side chain.
[g]Avoid if ceftriaxone allergy because of shared/similar R1 side chain.
[h]Avoid if cefoxitin allergy because of shared/similar R1 side chain.
[i]Avoid if ceftazadime allergy because of shared/similar R1 side chain.
[i]Avoid if cefepime allergy because of shared/similar R1 side chain.
[k]Avoid if aztreonam allergy because of shared/similar R1 side chain.

patch testing and knowledge of antibiotic cross-reactivity (Table 3). [79,152,167–174]

(4) In acute settings, of mild to moderate rash without fever, mucosal or internal organ involvement, antimicrobials can be continued with close monitoring.

T-CELL DIAGNOSTICS

Lymphocyte transformation test

Ex-vivo investigations have been explored for T cell-mediated ADRs, including the lymphocyte transformation test (LTT). LTT has a reported sensitivity of 27–70% and specificity of 72.7–100%, but, remains hindered by testing time, requirement for radioactive materials, and potential dependence on B-cell proliferation [8,175–177]. LTT has been used for causality assessments in ceftriaxone, ampicillin/sulbactam, and metronidazole-associated linear IgA disease, ceftriaxone-associated MPE, penicillin/amoxicillin-induced MPE, and ceftazidine-induced DRESS [178–181]. In a small study of amoxicillin-induced immune-mediated ADR, correlation between positive in-vivo IDT and LTT was not demonstrated [182]. LTT has also been used in a small number of other case reports/series for immune-mediated ADRs secondary to antituberculosis therapies [129], aminopenicillins [122,123,177], cephalosporins [183], and antistaphylococcal penicillins [137].

RECOMMENDATION

(1) Antibiotic LTT is an unvalidated test that has been associated with both false positive and false negative results and currently remains a research tool used in specialized centers for the investigation of T cell-mediated ADRs.

Enzyme-linked immunospot assay

Enzyme-linked immunospot (ELISpot) is an ex-vivo technique used to analyze low-frequency antigen-specific, cytokine-producing (e.g., IFNγ) cells in peripheral blood following exposure to pharmacological drug concentrations [8]. ELISpot can be employed for a range of cytokine responses depending on the underlying drug hypersensitivity immunopathogenesis. For example, AGEP can have high IL-13 and IFNγ, FDE raises IL-10, whereas DRESS can have high IL-5 or IFNγ [60,184]. ELISpots measuring granzyme have also been employed [175]. ELISpot studies have demonstrated that 1 : 150 to 1 : 5000 T cells remain 'reactive' in patients after ADR for up to 12–20 years [60,185]. ELISpot has also been shown to have better sensitivity than LTT in detecting drug-specific T-cell responses [185,186]. Nonetheless, ELISpot has only been employed in research settings for the investigation of antimicrobial allergy. Estimations of sensitivity and specificity are flawed because of the absence of a reference gold standard. However, increasing the drug concentration used to stimulate the patients' cells and increasing

incubation periods (48 h versus overnight) have been shown to increase assay sensitivity without decreasing specificity. An examination of ELISpot use in antimicrobial T cell-mediated ADRs is outlined below.

ENZYME-LINKED IMMUNOSPOT AND ANTIVIRAL IMMUNE-MEDIATED ADVERSE DRUG REACTIONS

ELISpot is described in studies examining antiretroviral hypersensitivity reactions, notably abacavir and nevirapine. ELISpot has been used to detect abacavir hypersensitivity in patients that are HLA-B*57:01 negative [187]. IFNγ ELISpot has also been used to demonstrate that abacavir unexposed HLA-B*57:01 positive patients have a 'resting' abacavir reactive $CD8^+$ T-cell population [188▪]. In nevirapine hypersensitivity reactions, IFNγ ELISpot has been utilized to demonstrate that specific combinations of $CD4^+$ class II-restricted and $CD8^+$ class I-restricted T cells contribute to the hypersensitivity immunopathogenesis [189].

ENZYME-LINKED IMMUNOSPOT AND ANTIBIOTIC IMMUNE-MEDIATED ADVERSE DRUG REACTIONS

Penicillins

Earlier studies demonstrate that ELISpot IFNγ testing was positive in patients with a history of amoxicillin immune-mediated ADRs [185,190]. No positive ELISpot results were identified in control patients or those with a history of IgE-mediated disease, highlighting the specificity of the test. The intensity of response was, however, proportional to time after diagnosis. The overall sensitivity and specificity was 91 and 95%, respectively. Khalil *et al.* [190] demonstrated a sensitivity and specificity of 80 and 100%, respectively for ELISpot measuring IL-2, IL-5, and IFNγ in patients with amoxicillin immune-mediated ADR. Rozieres *et al.* [185] demonstrated ex-vivo effectiveness for other β-lactams, including ticarcillin [191]. ELISpot has also been used in models using antigen-specific T-cell clones to confirm patients with a history to piperacillin hypersensitivity [192].

Cephalosporins

Tanvarasethee *et al.* [193] examined the use of ELISpot to diagnose cephalosporin-induced MPE and compare against SPT, delayed-IDT, and patch testing. From the 25 patients, 40% had a positive IFNγ and IL-5 response compared with 8% who had a positive delayed-IDT or patch testing ($P = 0.008$). There was a higher probability of positive ELISpot if performed within 2 years of reaction ($P = 0.046$) [193].

Other antimicrobials

The use of ELISpot for quinolones, glycopeptides, TMP-SMX, and other commonly used antibacterial therapy is absent. Aminoglycosides are an infrequent cause of SCARs, yet a case of amikacin-induced DRESS was confirmed on patch testing and ELISpot [194]. A case of sulfasalazine hypersensitivity syndrome was also confirmed with ELISpot [195]. The use in other antimicrobials is also ill-defined. Further research is required to evaluate this testing in a range of antimicrobial therapies.

RECOMMENDATION

(1) ELISpot remains a test available only in specialized centers for the investigation of T cell-mediated ADRs.

PREDICTING T-CELL RESPONSES: HUMAN LEUKOCYTE ANTIGEN TYPING

Recently, an increasing number of antimicrobial immune-mediated ADRs have been associated with various HLA alleles (Table 4). In general, because of varying HLA allele frequencies, different ethnic populations have different genetic associations. To date, the best characterized antimicrobial-induced, HLA-associated immune-mediated ADRs that appear to generalize across populations include AHS and nevirapine SCARs. The association between AHS and HLA-B*57:01 resulted in the implementation of a routine screening test that is widely employed in the developed world before abacavir treatment. Before widespread acceptance, the HLA-B*57:01 genetic association with abacavir was established in a large population with a diverse genetic background. This screening test has a positive predictive value of 55% and a NPV of 100%, which is crucial for drug safety [218–220]. Less than 100% NPVs and very low positive predictive values of other antimicrobial drug hypersensitivity HLA associations have limited their translation into routine clinical practice as screening tests. For example, although only 13 individuals would need to be screened for HLA-B*57:01 to prevent a single case of AHS, over 14 000 individuals would have to be tested for this same allele to prevent a single case of flucloxacillin-associated hepatitis.

The story of nevirapine-induced immune-mediated ADRs is quite complex. Nevirapine-induced

Table 4. Human leukocyte antigen associations for antimicrobial associated T cell-mediated hypersensitivity syndromes

Antimicrobial	Clinical presentation	Associated HLA allele (s)	Population	NPV	PPV	NNT
Abacavir	Hypersensitivity syndrome (fever, rash, GI distress, malaise)	HLA-B*57:01	European, African	100% for patch test confirmed	55%	13
Efavirenz	Rash	HLA-DRB1*01	French			ND
Nevirapine	Rash	HLA-B*35:05	Thai, African, Asian, European, Thai	97%	16%	ND
		HLA*Cw4				
	DRESS	HLA-B*14/Cw8	Italian			
		HLA-Cw8	Japanese			
		HLA-Cw*4 and HLA-DRB1*15	Han Chinese			
		HLA-B*3505	Asian			
		HLA-B*3501 and HLA-B*15/DRB1*15	Australian			
	Hepatitis	HLA-DRB1*01:01	Australian, European	96%	18%	
		HLA-DRB1*01:02	South African			
	SJS/TEN	HLA-C*04:01	Malawian			
Dapsone	Rash, hepatitis	HLA-B*13:01	Chinese	99.8%	7.8%	84
Flucloxacillin	Hepatitis (DILI)	HLA-B*57:01	European	99.99%	0.12%	13819
		HLA-DRB1*0107-DQB1*0103				
Amoxicillin-clavulanate; coamoxiclav	Hepatitis (cholestatic)	HLA*02:01	European			ND
		HLA-DQB1*0602 and rs3135388, a tag SNP of HLA-DRB*15:01-DQB1*06:02				ND
Sulfamethoxazole	SJS/TEN	HLA-B*38	European			ND
	FDE	HLA-A*30-B*14-Cw*6 haplotype	Turkish			
Aminopenicillins	Rash	HLA-A*2	Italian			ND
		HLA-DR*52				
Sulfonamides	SJS/TEN	HLA-A*29	European			ND
		HLA-B*12				
		HLA-DR7				
Isoniazid	DILI	NAT2 slow acetylator, CYP2E1*5 and *1B	European			ND
	Drug-induced lupus erythematous	HLA-DR*4	Italian			
Levamisole	Agranulocytosis	HLA-B*27	South American			ND

DILI, drug-induced liver injury; DRESS, drug reaction with eosinophilia and systemic symptoms; FDE, fixed drug eruption; GI, gastrointestinal; HLA, human leukocyte antigen; ND, no data; NNT, number needed to treat; NPV, negative predictive value; PPV, positive predictive value; SJS/TEN, Stevens–Johnson syndrome/toxic epidermal necrolysis.
Reproduced with permission from [196–221].

immune-mediated ADRs have been associated with different HLA alleles across different ethnic populations. These HLA associations appear to be phenotype specific and involve both class I and class II HLA alleles. An association between nevirapine-induced hepatitis and HLA-DRB1*01:01 was first reported in a Western Australian population [217] and has since been reported in other Caucasian populations [216]. The closely related allele HLA-DRB1*01:02 was associated with nevirapine-induced hepatitis in a South African cohort [196]. Nevirapine DRESS has been associated with the HLA-Cw*8 or

Cw*8-B*14 haplotype in Japanese and Italian populations and also with HLA-Cw*4 and HLA–DRB1*15 in Han Chinese, HLA-B*35:05 in Asians, and HLA-B*35:01 and HLA-B*15/DRB1*15 in an Australian cohort [189,212–215]. Many of these alleles including HLA-DRB*01, HLA-Cw*04 and HLA-B*35:05 are also associated with nevirapine-induced rash [209–211,215,216].

Other HLA associations have been described for immune-mediated ADRs to efavirenz, dapsone, flucloxacillin, amoxicillin-clavulanante, sulfamethoxazole, aminopenicillins, sulfonamides, isoniazid, and levamisole (Table 4).

Many of these antimicrobials such as flucoxacillin and amoxicillin-clavulanate are specifically associated with drug-induced liver injury, which can be associated with fulminant hepatic failure [220]. Although few HLA screening tests have advanced to the level of routine clinical practice, HLA associations have significantly advanced our understanding of the immunopathogenesis of immune-mediated ADRs.

RECOMMENDATION

(1) Level IA evidence exists to support screening for HLA-B*57:01 prior to initiation of abacavir therapy. This screening test has a 100% NPV and is widely recommended as part of guideline-based practice.

CROSS REACTIVITY IN T CELL-MEDIATED REACTIONS

In settings where in-vivo and ex-vivo diagnostics are unavailable, understanding cross-reactivity based on shared chemical structure among antimicrobials is essential (Table 3). Most of the rates of cross-reactivity for delayed immune-mediated ADRs are extrapolated from data that exist for cross-reactivity in the setting of immediate hypersensitivities. Earlier reports of high rates of penicillin/cephalosporin cross-reactivity were confounded by penicillin contamination of cephalosporin manufacturing [2,3,222]. Current literature supports that most cross-reactivity that occurs in the β-lactam class occurs on the basis of shared R1 and/or R2 side chains [85,149,150]. Recent reports suggest patients with a history of delayed hypersensitivity to aminopenicillins most commonly cross-react with aminocephalosporins sharing an R1 group such as cephalexin, cefaclor, and cephadroxil and generally tolerate all other cephalosporins [223,224]. Challenging patients with a penicillin/amoxicillin allergy history with a cephalosporin not sharing the same side chain (e.g., cefuroxime or ceftriaxone) proved successful in a study of 41 patients by Novalbas *et al.* [225]. The rate of cross-reactivity between penicillin and third-generation cephalosporins now approaches 1%, a far cry from 10–25% initially quoted in very early studies [226]. Romano *et al.* [169] demonstrated that patients with cephalosporin immediate hypersensitivity can still be safely treated with compounds that have side-chain determinants different from those of the responsible cephalosporin.

Cross-reactivity between carbapenems has been infrequently reported [227]; a shared T-cell epitope remains unknown [227]. Cross-reactivity between macrolides also appears rare, with infrequent reports of immediate cross-reactivity noted particularly between those with 14-membered ring such as erythromycin, clarithromycin, and roxithromycin and the 15-membered azalide, azithromycin [228]. T cell-mediated cross-reactivity between tetracyclines [229], in particular doxycycline and minocycline has been reported [229]. Cross-reactivity [230] and tolerance [231] have been reported for aminoglycoside antibiotics in which ADRs are more common for topical than systemic agents because of contact sensitization [194,232]. For nitroimidazoles (e.g., metronidazole, tindazole) T cell-mediated ADRs have been reported, with cross-reactivity noted [94–96,233].

Delayed immune-mediated ADRs are less frequent than immediate ADRs in regards to quinolones [234], with cross-reactivity more commonly occurring between first and second-generation quinolones than third and fourth generation [234–237]. Glycopeptide (vancomycin and teicoplanin) cross-reactivity is also reported [238–240], but remains controversial, with many reports extrapolated from reoccurrence of hematological disturbances. Patients with isolated vancomycin hypersensitivity have also been known to tolerate teicoplanin [97,238,241–243].

An estimated 3–6% of the population is considered 'allergic' to sulfonamides, with TMP/SMX the most commonly implicated example [244]. Although belief in overall sulfonamide cross-reactivity persists [245], recent reviews do not support cross-reactivity between antibacterial and nonantibacterial sulfonamides [244,246–249]. There is cross-reactivity between antibiotic sulfonamides, especially sulfasalazine and sulfamethoxazole [250]. The nonantibacterial sulfonamides (e.g., azetazolamide, forusemide, celecoxib, thiazide diuretics, sumatriptan, sotalol, probenacid) do not contain the structural region known to cause the allergic response (i.e., N1 heterocyclic ring; an N-containing ring attached to the N1 nitrogen of the sulfonamide group and arylamine group at the

N4 position). Although early reports questioned the potential for cross-reactivity between TMP-SMX and darunavir [249,251,252], authors have noted an absence of TMP-SMX allergy history in those with darunavir hypersensitivity [253–255]. Notably patients with a history of sulfa antimicrobial allergy were not excluded from darunavir clinical trials.

The potential for cross-reactivity between dapsone and TMP-SMX is now somewhat controversial with most reports occurring in HIV-infected individuals without evidence of positive rechallenge. The current estimated rate of cross-reactivity is less than previously reported (9–11% versus 20–45%) [256,257]. In those requiring TMP-SMX therapy with a history of non-SCAR ADR to antibacterial sulfonamide, we recommend a supervised oral rechallenge, rather than drug avoidance [258,259].

Antiretroviral

Cross-reactivity between most antiretroviral classes is likely very low because of the lack of structural similarities. However, patients with prior severe hypersensitivity to an NNRTI should be monitored if new NNRTI therapy is initiated. Mehta and Maartens [260] reported recurrent reactions in 12.6% of patients with reported rash who were switched from nevirapine to efavirenz, compared with 50% of patients switched from efavirenz to nevirapine. Cross-reactivity is reported to be higher between nevirapine and delavirdine, which have a similar structure, but delavirdine is not currently used because of its difficult dosing, pill burden, drug interactions, and lower efficacy compared with contemporary NNRTIs [261].

Recommendations for antimicrobial use, in relation to likely cross-reactivity, in patients with delayed hypersensitivities to isolate antimicrobials are given in Table 3.

CONCLUSION

In an era of increasing antimicrobial resistance and use of broad-spectrum antimicrobial therapy, ensuring patients are correctly 'labeled' in respect to antimicrobial-associated immune-mediated ADRs is essential. Reexposure to the implicated antimicrobial, especially in the setting of SCARs and AHS, is associated with significant morbidity and mortality.

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Conflicts of interest

There are no conflicts of interest.

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